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# OPTIMUM TIME FOR ADMINISTRATION OF PROTAMINE ZINC INSULIN

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NEW YORK

Hagedorn, Norman Jensen, Krarup and Wodstrup,[1] who were the first to use protamine insulin, gave in most of their cases a dose of protamine insulin in the evening and one of regular insulin in the morning. The addition of zinc to protamine insulin by Scott and Fisher[2] prolonged the action of the new preparation considerably, so that a single injection a day was sufficient to control the diabetes in a large percentage of cases. Sprague and his associates[3] adopted the procedure of giving the single dose of protamine zinc insulin early in the morning, and their method was soon followed by most investigators (Campbell and his associates,[4] Joslin,[5] Rabinowitch[6] and others).

In previous studies (Mosenthal[7] and Mark, Sackey and Mosenthal[8]) in which a single dose of protamine zinc insulin was administered at 6 or 7 a. m., it was found that there was a rise of the level of sugar

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1. Hagedorn, H. C.; Norman Jensen, B.; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**:177-180 (Jan. 18) 1936.

2. Scott, D. A., and Fisher, A. M.: Studies on Insulin with Protamine, J. Pharmacol. & Exper. Therap. **58**:78-92 (Sept.) 1936.

3. Sprague, R. G.; Blum, B. B.; Osterberg, A. E.; Kepler, E. J., and Wilder, R. M.: Clinical Investigations with Insulin Protamine Compound, Proc. Staff Meet., Mayo Clin. **11**:257-258 (April 22) 1936.

4. Campbell, W. R.; Fletcher, A. A., and Kerr, R. B.: Protamine Insulin in the Treatment of Diabetes Mellitus, Tr. A. Am. Physicians **51**:161-173, 1936.

5. Joslin, E. P.; Root, H. F.; Marble, A.; White, P.; Joslin, A. P., and Lynch, G. W.: Protamine Insulin, Tr. A. Am. Physicians **51**:174-187, 1936.

6. Rabinowitch, I. M.; Foster, J. S.; Fowler, A. F., and Corcoran, A. C.: Clinical Experiences with Protamine Zinc Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, Canad. M. A. J. **35**:239-252 (Sept.) 1936.

7. Mosenthal, H. O.: Protamine Zinc Insulin, J. A. M. A. **110**:87-90 (Jan. 8) 1938.

8. Mark, M. F.; Sackey, M. S., and Mosenthal, H. O.: Protamine Zinc Insulin in the Treatment of Diabetes Complicated by Tuberculosis, Quart. Bull., Sea View Hosp. **2**:357-362 (July) 1937.

in the blood after each meal and that the lowest determinations were those obtained at 3 or at 6 a. m. At that time it was felt that the reason for the low values for sugar during the early morning hours was not that the maximum effect of the insulin occurred twenty-one to twenty-four hours after injection but rather that food was withheld during the night. Obviously, it would be a fortunate circumstance if the low blood sugar values during the night did represent the maximum effect of the insulin at that time, since, if this were the case, the early morning hypoglycemic reaction and the postprandial hyperglycemia that so commonly occur in severe diabetes could be eliminated by changing the time of administration of the insulin.

Lawrence and Archer,[9] who, like most investigators, found that many patients with severe diabetes could not do well with a single dose of protamine zinc insulin in the morning, reported satisfactory results in 6 cases when the insulin was given at bedtime. Their explanation was that when the insulin was administered at night, its minimum action coincided with the hours of sleep and its maximum with the intake of the day's food. They, however, said they believed that most patients obtain better control when protamine zinc insulin, with or without the addition of a dose of regular or soluble insulin, is given before breakfast. Joslin[10] has quoted a personal communication from Himsworth, who claimed to have obtained excellent results by administering protamine zinc insulin at 11 p. m. It appeared that the food was far better utilized the following morning than if the protamine zinc insulin were given before breakfast.

As my associates and I were unable to observe any striking change in the character of the control of diabetes in a few cases by altering the time of administration of protamine zinc insulin from morning to night, the present study was carried out in order to arrive at a definite conclusion as to the optimum time of day for the injection.

## MATERIAL

The work was done in the metabolic service at Sea View Hospital on 6 patients who, in addition to diabetes, had pulmonary tuberculosis. Since these patients were hospitalized for a long period, they could be kept under constant and careful observation. In order to eliminate the changes incident to variations in body temperature, only afebrile patients were selected.

The patients were on a diet having a carbohydrate value of 150 to 200 Gm. Four meals a day were given (at 7:30 a. m., 11:30 a. m., 4:30 p. m. and 8:30 p. m.) with the carbohydrate divided so that 25 per cent was allowed at breakfast and at lunch, 35 per cent at dinner and 15 per cent at 8:30 p. m. Determinations of the blood sugar value were made at frequent intervals throughout the twenty-four hours by the capillary method of Folin-Malmros. For 3 of the

9. Lawrence, R. D., and Archer, N.: Zinc Protamine Insulin: A Clinical Trial of the New Preparation, Brit. M. J. **1**:487-491 (March 6) 1937.

10. Joslin, E. P.: Protamine Insulin, J. A. M. A. **109**:497-503 (Aug. 14) 1937.

patients four blood sugar curves were obtained with the insulin administered in one dose at 6 or 7 a. m., 11 a. m., 4 p. m. and 8 p. m., respectively. In 1 case two curves were obtained with the insulin injected at 7 a. m. and 8 p. m. In 2 others the insulin was administered at 7 a. m. and 11 p. m. In each instance one dose of insulin for the twenty-four hours was given. The curves were made only after the patients had been on a specific regimen for more than a week, in order to eliminate the possible effect of the cumulative action of the insulin given under the preceding method of therapy.

## REPORT OF CASES

The cases studied are briefly summarized as follows:

CASE 1.—E. G., a woman aged 42, was admitted to the hospital on May 6, 1934. Pulmonary tuberculosis was first diagnosed in 1924. Diabetes mellitus

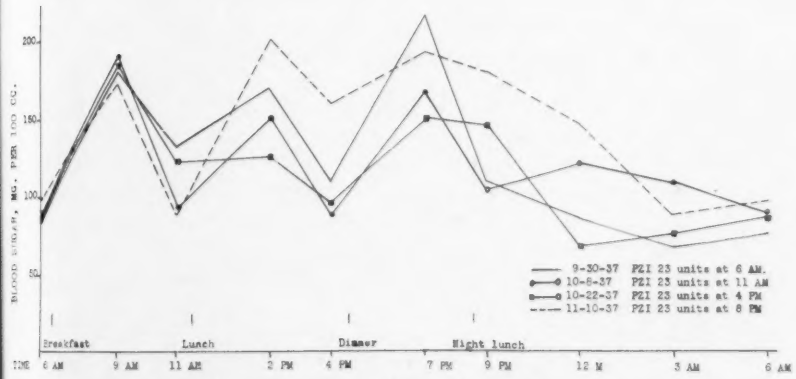


Chart 1 (case 1).—Superimposed blood sugar curves made when protamine zinc insulin was given at 6 a. m., 11 a. m., 4 p. m. and 8 p. m., respectively. Note the marked similarity of the curves.

was discovered during her stay at the hospital in January 1936. The tuberculosis became arrested after thoracoplasty performed in September 1934. Beginning in November 1936 the diabetes was controlled with a diet of 200 Gm. of carbohydrate, 110 Gm. of fat and 90 Gm. of protein and with 23 units of protamine zinc insulin given at 6 a. m. A blood sugar curve was made on Sept. 30, 1937. On October 1 the time of administration of insulin was changed to 11 a. m., and a second curve was obtained on October 8. The time of the injection of insulin was then changed to 4 p. m., and a third curve was obtained on October 22. Beginning on October 23, the insulin was given at 8 p. m., and a fourth curve was obtained on November 10. The four curves are superimposed in chart 1. The diabetes was under perfect control throughout the experiment.

*Comment.*—From chart 1 it is evident that, regardless of the time of administration of the insulin, the blood sugar curves in this instance were strikingly similar.

Case 2.—H. D., a woman aged 52, was admitted to the hospital on Nov. 11, 1936. Diabetes mellitus was discovered in June 1934. Symptoms of pulmonary tuberculosis were noted in November 1935. Pneumothorax was started on the right side in November 1936, and the sputum became free from bacilli in June 1937. Shortly after the patient's admission to the hospital the diabetes was controlled with a diet of 150 Gm. of carbohydrate, 110 Gm. of fat and 90 Gm. of protein and with 30-20-20 units of regular insulin daily. Protamine zinc insulin was first used on Jan. 27, 1937, and after stabilization the diabetes was perfectly controlled with a single dose of 35 units of protamine zinc insulin given at 7 a. m. A blood sugar curve was made on March 6. The time of the injection was changed on October 1 to 11 a. m., and a second curve was obtained on October 8. Beginning on October 13, the protamine zinc insulin was given at 4 p. m., and a third curve

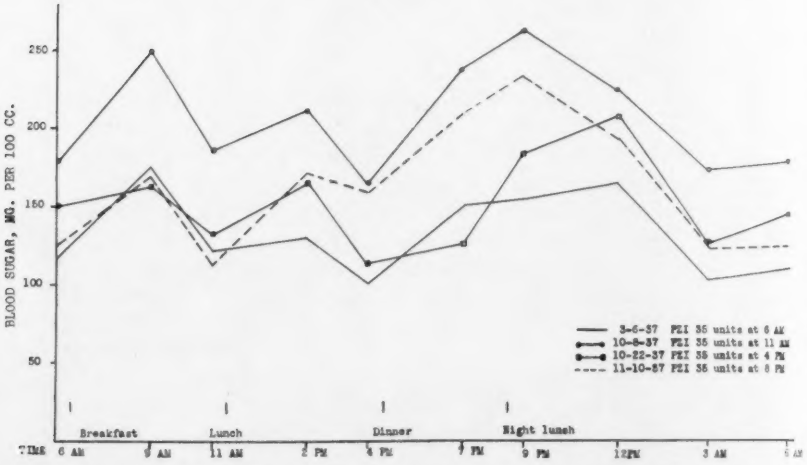


Chart 2 (case 2).—Superimposed blood sugar curves made when protamine zinc insulin was given in one dose at 6 a. m., 11 a. m., 4 p. m. and 8 p. m., respectively. There is a marked similarity in the character of the curves regardless of the time of administration of the insulin. Note the elevation of the blood sugar value after each meal and the low value just before meals and during the night.

was made on October 22. The time of administration of insulin was changed on October 24 to 8 p. m., and a fourth curve was obtained on November 10. The urine was free from sugar throughout the experiment. The blood sugar curves are superimposed in chart 2.

Case 3.—M. M., a woman aged 61, was found to have diabetes in 1932. Pulmonary tuberculosis was discovered in February 1936. The tuberculosis apparently became arrested in September 1936. The diabetes was well controlled

with a diet of 200 Gm. of carbohydrate, 110 Gm. of fat and 90 Gm. of protein and with 40 units of protamine zinc insulin given at 6 a. m. A blood sugar curve was obtained on April 16, 1937. A second curve was made on October 8, after the patient had been receiving 30 units of protamine zinc insulin at 11 a. m. Because the blood sugar level was elevated, the dose of insulin was raised to 35 units, and beginning on October 12, this was given at 4 p. m. On October 22 a third curve was obtained. The time of administration of insulin was then changed to 8 p. m., and a fourth curve was made on November 10. The urine remained free from sugar throughout.

*Comment.*—The superimposed curves are shown in chart 3. Although there are minor variations in the character of the curves, the general similarity is apparent.

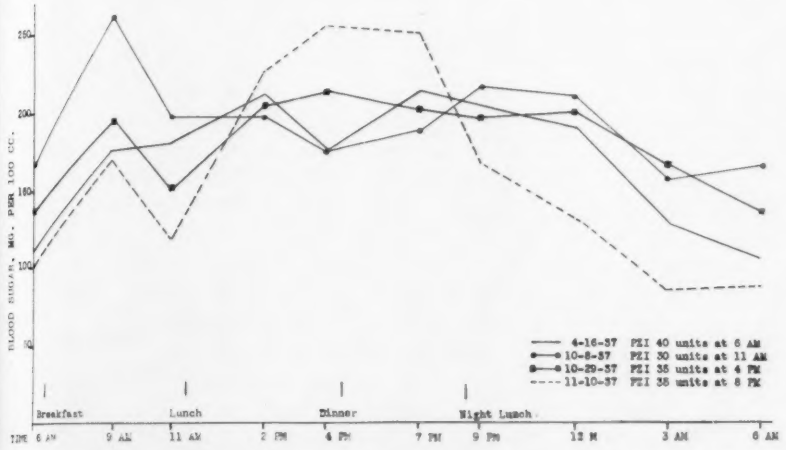


Chart 3 (case 3).—Superimposed blood sugar curves made when protamine zinc insulin was given in one dose at 6 a. m., 11 a. m., 4 p. m. and 8 p. m., respectively. Note that although there are some variations, there is a general similarity in the character of the curves.

CASE 4.—N. A., a woman aged 67, was admitted to the hospital on May 29, 1936. Symptoms of diabetes mellitus appeared in 1932, and pulmonary tuberculosis was discovered in January 1936. The patient had been receiving liver extract for pernicious anemia since March 1931. From the time of her admission to the hospital until March 15, 1937, the diabetic condition was controlled with a diet of 150 Gm. of carbohydrate, 110 Gm. of fat and 90 Gm. of protein and with 25-10-15 units of regular insulin. At that time the use of protamine zinc insulin was begun, and she was receiving a single injection of 50 units at 7 a. m. In April the dose of insulin was raised to 70 units, and the injection was continued at 7 a. m. A blood sugar curve was obtained on December 4. The time of administration was changed to 8 p. m. on December 6, and a second curve was made on December 22. The two curves are superimposed in chart 4. The urine was free from sugar on the day each of the curves was taken.

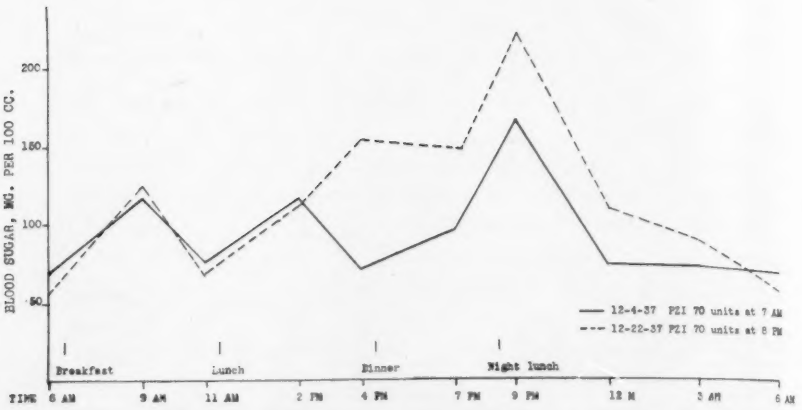
BLOOD SUGAR, MG. PER 100 CC.
200
150
100
50
12-4-37 PZI 70 units at 7 AM
12-22-37 PZI 70 units at 8 PM
Breakfast
Lunch
Dinner
Night lunch
TIME 6 AM 9 AM 11 AM 2 PM 4 PM 7 PM 9 PM 12 M 3 AM 6 AM

Chart 4 (case 4).—Superimposed blood sugar curves made when protamine zinc insulin was given in one dose at 7 a. m. and at 8 p. m.

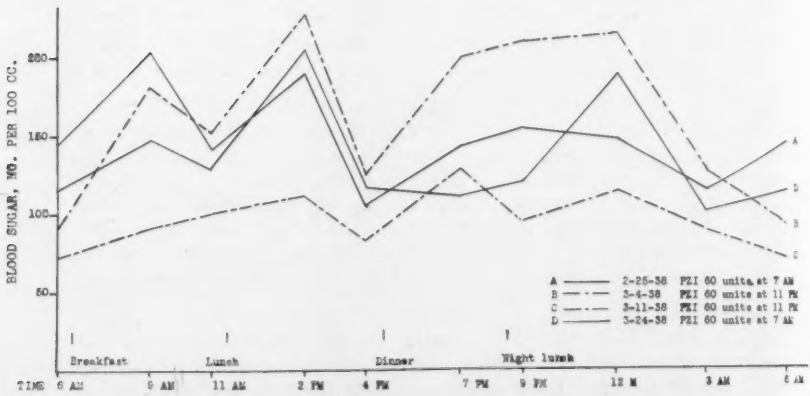
BLOOD SUGAR, MG. PER 100 CC.
200
150
100
50
A 2-25-38 PZI 60 units at 7 AM
B 3-4-38 PZI 60 units at 11 PM
C 3-11-38 PZI 60 units at 11 PM
D 3-24-38 PZI 60 units at 7 AM
Breakfast
Lunch
Dinner
Night lunch
TIME 6 AM 9 AM 11 AM 2 PM 4 PM 7 PM 9 PM 12 M 3 AM 6 AM

Chart 5 (case 5).—Curves *A* and *D* were obtained when the patient was receiving protamine zinc insulin at 7 a. m. Curves *B* and *C* were made when the insulin was given at 11 p. m. If only curves *A* and *B* are compared, it appears that there is better utilization of carbohydrate in the morning when the insulin is given at night. However, when curves *C* and *D* are compared, it is evident that there may be considerable variation in the character of the blood sugar curves even though the patient remains on the same plan of therapy.

CASE 5.—A. M., a man aged 53, was admitted to the hospital on Nov. 1, 1937. Diabetes mellitus was discovered in January 1937; at that time symptoms of pulmonary tuberculosis appeared. The patient was receiving a diet of 150 Gm. of carbohydrate, 110 Gm. of fat and 90 Gm. of protein; 60 units of protamine zinc insulin was being given at 7 a. m. The first blood sugar curve (chart 5, curve *A*) was taken on February 25, 1938. The time of injection of insulin was changed on February 26 to 11 p. m., and curve *B* was obtained on March 4. Because there appeared to be a considerable difference in the levels of blood sugar under the two plans of therapy, it was decided to repeat the study. Consequently, the patient continued to receive insulin at 11 p. m., and curve *C* was obtained on March 11. There was considerable difference between this curve and curve *B*, although the two were taken with the patient under the same regimen. Beginning on March 14, the time of administration of insulin was changed to 7 a. m., and curve *D* was made on March 25. The urine remained free from sugar throughout the experiment.

*Comment.*—A study of the curves in this case reveals the fact that the blood sugar values do not remain constant from day to day even though the patient receives the same diet and the same dose of insulin, given at the same time. If curves *A* and *B* are compared, it appears that in the morning the blood sugar value is lower when the insulin is given at 11 p. m.; but, on the other hand, if curves *B* and *D* are compared, little difference is seen in the blood sugar values in the morning. The values were low throughout the day at the time curve *C* was obtained. It is well to compare this curve with curve *B*. There is a marked difference between the two, although the patient was on the same plan of therapy at the time these were taken. Obviously, therefore, one cannot arrive at a definite conclusion on the basis of a single observation. It seems reasonable to assume that the variations in the curves are variations that are likely to occur, particularly in severe diabetes, from day to day and are not the result of a change in the time of the injection of insulin.

CASE 6.—M. F., a man aged 44, was admitted to Sea View Hospital on May 27, 1937. Diabetes mellitus was discovered in 1932. Symptoms of pulmonary tuberculosis appeared in December 1936. The diabetes was at first perfectly controlled with a diet of 150 Gm. of carbohydrate, 110 Gm. of fat and 90 Gm. of protein and with 50-25-30 units of regular insulin. The use of protamine zinc insulin was begun on July 7, 1937, and after stabilization the urine remained free from sugar with the injection of 65 units at 7 a. m. On Feb. 25, 1938, a blood sugar curve was obtained (chart 6, curve *A*). On February 26 the time of the injection of insulin was changed from 7 a. m. to 11 p. m., and a second curve was made on March 4. In this case also there appeared to be a marked difference in the blood sugar values, the value in the morning being considerably lower when the insulin was given at 11 p. m. Because of this observation it was decided to repeat the determinations. The patient continued to receive the insulin at 11 p. m., and a third curve was obtained on March 11. The time of injection was then changed to 7 a. m., and a fourth curve was obtained on March 25.

*Comment.*—In this instance, more so than in case 5, there was a marked difference in the blood sugar values in the morning (curves *A* and *B*). If only these two curves had been made, the obvious conclusion would have been that there was much better utilization of dextrose the next morning when the protamine zinc insulin was given at 11 p. m. However, if curves *B* and *D* are compared, there appears to have been better utilization of carbohydrate in the morning when insulin was given at 7 a. m. There was considerable difference in the blood sugar values on the days that curves *B* and *C* were made, although the patient was receiving the insulin at 11 p. m. on both occasions.

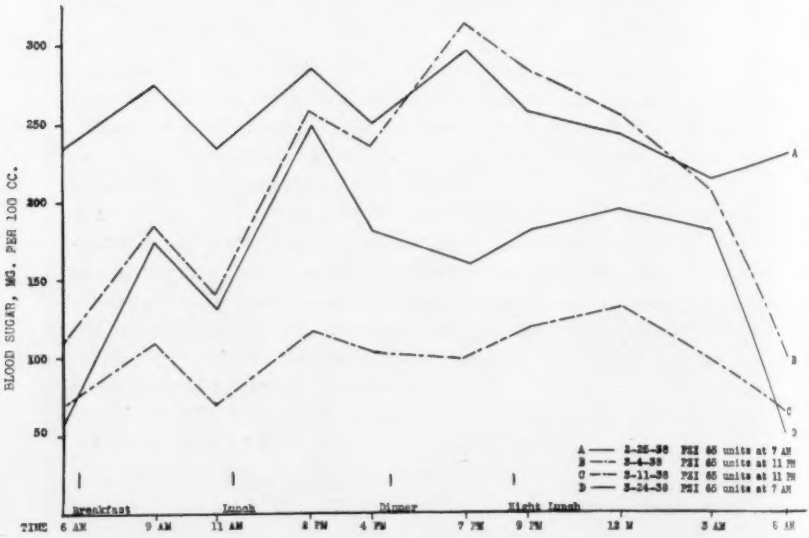


Chart 6 (case 6).—Curves *A* and *D* were made when protamine zinc insulin was administered at 7 a. m. Curves *B* and *C* were made when the insulin was given at 11 p. m. Note the variations in the character of the curves even when the patient was kept on the same regimen.

Similarly, there is a marked difference between curves *A* and *D*, although the insulin in both instances was administered at 7 a. m.

It appears from the findings in cases 5 and 6 that one can expect considerable variations in the blood sugar curves from day to day, independent of the time of administration of the insulin.

## COMMENT

Examination of the superimposed blood sugar curves in cases of mild and moderately severe diabetes (cases 1 to 3) reveals the fact that the curves are remarkably similar regardless of the time of admin-

istration of protamine zinc insulin. Minor variations occur, to be sure, but these are no greater than the variations observed when several curves are taken for a patient who remains on the same plan of therapy. The changes can be explained by alterations in intestinal absorption and by changes in the emotional status of the patient.

Obviously, then, it appears, at least in mild and moderately severe diabetes, that the single dose of protamine zinc insulin may be administered at whatever time of day the patient prefers. This, of course, is a definite advantage in the use of the new insulin, since it further relieves the patient of the necessity of living the "time-table sort of existence" that is so essential with the use of regular insulin.

Of the 3 cases of severe diabetes studied, in 1 case (case 4) the blood sugar curves were much alike, and certainly in this instance altering the time of administration of insulin had no effect on the character of the control. In 2 other cases of severe diabetes (cases 5 and 6) it first appeared that there was better utilization of carbohydrate in the morning when insulin was given at night. However, on repetition of the blood sugar studies, the findings suggested that there is considerable variation in the character of the curves from time to time even though the patient remains on the same plan of therapy and that these changes cannot be attributed to alteration in the time of administration of protamine zinc insulin. I am inclined to believe that in cases of severe as well as mild diabetes protamine zinc insulin may be given at any time of day. This opinion is further supported by the fact that in several other cases of severe diabetes, in which blood sugar curves had not been made, altering the time of administration of insulin had no appreciable effect on the glycosuria or the time of appearance of hypoglycemic reactions.

Rabinowitch [6] has shown that when protamine zinc insulin is given to a patient during fasting, the blood sugar value drops within a few hours to a low point and then remains at a practically constant level for at least thirty-six hours. Examination of the curves in the present study reveals the fact that the lowest values are those obtained just before breakfast, before lunch, before dinner and during the night, that is, during the fasting periods of the day. Furthermore, it is interesting to note that the blood sugar values at these times tend to approach the same level. From this observation, it may be concluded that the probable action of protamine zinc insulin is as follows: It lowers the blood sugar value to a certain level and tends to maintain it at that level for more than thirty-six hours. The larger the dose of protamine zinc insulin, the lower the basic level. The absorption of carbohydrate elevates the blood sugar value, but within a few hours in the cases of mild and moderately severe diabetes the basic level is again reached. Similarly, the basic level is maintained during any period

of fasting. The height to which the blood sugar value will be raised after meals will depend on the amount of carbohydrate taken and the severity of the diabetes. In severe diabetes the postprandial hyperglycemia may be so great that the slowly acting insulin is unable to cope with the situation, and, as a result, the high blood sugar value may be maintained throughout the day, and glycosuria may develop. During the night, however, when there is a prolonged period of fasting, the basic level will be attained.

If the conclusions as to the action of protamine zinc insulin are correct, one should not expect any change in the character of the blood sugar curve resulting from alteration in the time of administration of the insulin. In the patients studied, no appreciable variation was observed that could be attributed to such a change.

## SUMMARY AND CONCLUSIONS

A study of the effect on the blood sugar curve resulting from alteration in the time of administration of protamine zinc insulin was made in 6 cases of diabetes.

There was no appreciable effect on the character of the blood sugar curve resulting from a change in the time of injection of protamine zinc insulin.

Variations in the blood sugar levels may occur from day to day even when the patient remains on the same plan of therapy.

The single dose of protamine zinc insulin may be given at the time of day that is most convenient for the patient.

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# DELETERIOUS EFFECTS OF EXPERIMENTAL PROTAMINE INSULIN SHOCK

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The effects of hypoglycemia of long duration on the various tissues and on the organism as a whole are of fundamental importance. On the immediate practical side, the possibility of the use of excessive doses of the slowly acting protamine insulin by untrained persons (because of the lack of rapid action) or the accidental administration of the concentrated precipitate from a vial which has not been agitated makes essential a knowledge of the effects of hypoglycemia due to insulin shock. Insulin shock is being purposely used in the treatment of schizophrenia,[1] and undesirable effects of this use are also important.

In all of the experiments recorded here protamine zinc insulin of a strength of 40 units per cubic centimeter was used. It was administered subcutaneously. During some experiments [2] in which hyperalimentation was produced in albino rats by injections of protamine insulin, the first peculiar effects of hypoglycemia of even short duration were noticed. When the food box became empty or the dose of insulin was so large that the animals were unable to eat sufficient food to prevent the occurrence of hypoglycemia, insulin shock ensued, with the characteristic convulsions and coma. Determinations of the dextrose content of blood from the tail or from the heart by a method [3] which gives approximately true values for dextrose were found to range from 0 to 27 mg. per hundred cubic centimeters, depending on how near a convulsion (which would tend to raise the value) the specimen had been taken. No amount of dextrose in an appropriate concentration given by stomach tube or intraperitoneally would rescue these rats. The concentration of sugar in the blood was often checked, and even when it was raised to above 100 mg. per hundred centimeters and kept above this level the rats

From the Scripps Metabolic Clinic.

A preliminary report of some of the experiments described in this paper has been published (Proc. Soc. Exper. Biol. & Med. **36**:515, 1937).

1. Sakel, M.: Neue Behandlung der Schizophrenia, Vienna, M. Perles, 1935.

2. MacKay, E. M., and Callaway, J. W.: Hyperalimentation in Normal Animals Produced by Protamine Insulin, Proc. Soc. Exper. Biol. & Med. **36**:406, 1937.

3. Somogyi, M.: A Method for the Preparation of Blood Filtrates for the Determination of Sugar, J. Biol. Chem. **86**:655, 1930.

always died from ten minutes to four hours later. A total of 38 animals in such accidental or planned experiments were followed. The occasional death which occurred soon after sugar was administered will be considered in connection with the similar behavior of dogs. Almost all of the other rats died, apparently from respiratory failures, with hypoglycemia or with the sugar content of the blood raised to normal but without any effect on the symptoms. A variable degree of hemorrhagic edema of the lungs was always observed. Some time before death the pulmonary pathologic condition was evidenced by the oozing of blood-tinged serous fluid from the nostrils of the comatose rat. This recalled the behavior of rats which we had once observed after an overdose of epinephrine, and the possibility occurred to us that the effect of insulin was, at least in part, an overproduction of epinephrine during the hypoglycemia. Although we have been able to demonstrate high concentrations of epinephrine in the blood of the rats with insulin shock, we have been unable regularly to prevent the development of the pulmonary pathologic condition in insulin-treated rats by prior removal of the adrenal medullas with sufficient time allowed for regeneration of the cortical tissue. Further study of this pulmonary edema, which occurs as a result of prolonged hypoglycemia in the albino rat but not in dogs, is warranted. Histologically it is similar to the neuropathic pulmonary edema which occurs when both vagus nerves are cut in the rabbit or in the guinea pig.[4] This occurs regularly when the vagi are severed in the rat, but it is interesting in view of the effects of insulin that in our hands, at least, such a procedure causes no serious symptoms in the dog. However, Prof. Maurice B. Visscher wrote us that Dr. Victor Lorber, working in his department, has found that the pulmonary edema caused by vagotomy is not truly neuropathic. He has found that if one vagus nerve is cut below the recurrent laryngeal nerve and the other above it, the rat or guinea pig does not die. He concluded that the edema which follows bilateral cervical vagotomy is the same type as that which occurs in any type of tracheal obstruction.

When dogs were given protamine insulin in sufficient doses to maintain hypoglycemia for periods of thirty hours or more, often with no convulsions but only a condition of deep stupor, the administration of dextrose by stomach tube during this period gave rise to fatal convulsions. Bollman [5] has made similar observations. Six of our animals died in this manner. It also happened occasionally with the hypoglycemic rats. A typical protocol follows:

4. Farber, S.: Studies on Pulmonary Edema: I. The Consequences of Bilateral Cervical Vagotomy in the Rabbit, J. Exper. Med. **66**:397, 1937; Studies on Pulmonary Edema: II. The Pathogenesis of Neuropathic Pulmonary Edema, ibid. **66**:405, 1937.

5. Bollman, J. L., cited by Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **59**:341 (Feb.) 1937.

EXPERIMENT 1.—A mongrel bitch weighing 29 Kg. was kept without food for twenty-four hours, at the end of which period the value for blood sugar was 57 mg. per hundred cubic centimeters. Sixty units of protamine zinc insulin was given. At the end of one and one-half hours the value for sugar in the blood was 55 mg. At the end of ten hours the dog was nervous. After nineteen hours the value for blood sugar was 22 mg. Fifty units of insulin was given. At twenty-two hours the value for blood sugar was 23 mg. and the dog was comatose. At twenty-seven hours the value for blood sugar was 18 mg., and the animal made an occasional movement. At thirty-two hours the value for blood sugar was 6 mg. At forty-three hours the animal had a convulsion. At fifty hours the value for blood sugar was 22 mg., and the dog was in deep coma. At fifty-five hours the value for blood sugar was 15 mg. At sixty-one hours 200 cc. of a 25 per cent solution of dextrose was given by stomach tube. At sixty-one and one-quarter hours there was a convulsion. At sixty-one and one-half hours the value for blood sugar was 54 mg. and convulsions were almost continuous. At sixty-one and seven-tenths hours the animal died.

The convulsions and sudden death were similar to the results of administrations of water [6] to previously dehydrated rabbits. After a number of trials we were able to produce convulsions and sudden death in 1 comatose hypoglycemic dog by giving water alone. Four of 9 rats in which the experiment was tried were killed in this way. Bollman [5] found that dogs which died in such attacks showed multiple petechial hemorrhages scattered throughout the brain. We observed such hemorrhages in the brain of only 1 dog, and this animal did not die suddenly when dextrose was first given but lingered for nearly twenty hours. The causes of sudden death when dextrose is given in cases of hypoglycemia are probably sudden electrolyte shift and hemoconcentration superimposed on cerebral stasis and degenerative changes which have been produced in the nerve tissue.[7] Allen and Vicens [8] have recently pointed out that the effects of shock and of large doses of insulin are mutually aggravating. It is possible that when the organism dies from insulin poisoning, even after the sugar content of the blood has been restored to normal and without improvement in the general condition, the condition of circulatory shock which contributes to death from excessive doses of insulin, apart from the blood sugar level per se, is so serious that ultimately it would cause death under any circumstances. Death would be hastened in these conditions by the administration of strong solutions of dextrose or by any other therapy which would tend to alter the concentration of the body fluids too rapidly.

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7. Riggs, H. E., and Griffiths, J. O.: Pathologic Changes in the Nervous System Incident to Alterations in the Physiologic Dynamic Equilibrium of the Blood (Insulin Shock), Arch. Neurol. & Psychiat. **39**:643 (March) 1938.

8. Allen, F. M., and Vicens, C. A.: Surgical Treatment of Experimental Insulin Poisoning, Endocrinology **24**:230, 1939.

The most interesting of the deleterious effects of poisoning with protamine insulin are the evidences of permanent damage to the brain. This is hardly surprising in view of the importance of an adequate supply of carbohydrate for the metabolism of the brain cells. Marked hypoglycemia is known to depress the metabolism of the brain,[9] and degenerative changes have been observed in the ganglion cells of the brains of patients and animals given large amounts of insulin.[10] Both sensory and motor disturbances ensued as a result of long-continued hypoglycemia. We shall consider here only those animals in which the concentration of blood sugar had returned to normal for at least four days. Impairment of vision and hearing as well as complete blindness and deafness developed. In 2 instances there resulted incessant restlessness and a complete disorganization of the emotional complex. Motor disturbances were the most common, incoordination, spasticity and even paralyses resulting from the long lowered sugar content of the blood, with consequent reduction in the metabolism of the brain. Details of only 1 experiment are given in the typical protocols which follow:

EXPERIMENT 2.—A mongrel bitch weighing 20.1 Kg. was kept without food for two days and was then given 40 units of insulin. The value for blood sugar was 62 mg. per hundred cubic centimeters. At three hours this value was 51 mg., and at eight hours it was 33 mg. At eleven hours 20 units of insulin was given. At twenty-two hours the value for blood sugar was 20 mg. Twenty units of insulin was given. At twenty-six hours the value for blood sugar was 15 mg. Ten units of insulin was given. At twenty-eight hours there was a severe convulsion followed by coma. At thirty-eight hours the animal was still comatose, with an occasional convulsion. At forty-four hours the value for blood sugar was 8 mg.; 50 gm. of dextrose in 20 per cent solution was given by stomach tube. At fifty-four hours the animal was recovering slightly and was given 30 units of insulin. At fifty-eight hours the value for blood sugar was 0. There were numerous convulsions. At seventy hours the animal was still in coma, with occasional convulsions. At seventy-eight hours 10 units of insulin was given. There was no change in the animal's condition. At ninety hours 20 units of insulin and, in addition, 200 cc. of 1 per cent sodium chloride by stomach tube were given. At ninety-four hours the value for blood sugar was 6 mg. Two hundred cubic centimeters of saline solution was given. At one hundred

9. Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: The Mechanism of Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935. Himwich, H. E.; Bowman, R. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, Science **86**:271, 1937.

10. Wohlwill, F.: Ueber Hirnbefunde bei Insulin-Ueberdosierung, Klin. Wchnschr. **7**:344, 1928. Terplan, K.: Changes in the Brain in a Case of Fatal Insulin Shock, Arch. Path. **14**:131 (July) 1932. Bodechtel, G.: Der hypoglykämische Shock und seine Wirkung auf das Zentralnervensystem, zugleich ein Beitrag zu seiner Pathogenese, Deutsches Arch. f. klin. Med. **175**:188, 1933. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938. Moersch, F. P., and Kernohan, J. W.: Hypoglycemia: Neurologic and Neuropathologic Studies, ibid. **39**:242 (Feb.) 1938.

and two hours the animal was still in coma. Three hundred cubic centimeters of milk was given. At one hundred and ten hours the temperature was 36 C. (96.4.); 50 Gm. of dextrose in 300 cc. of milk was given. At one hundred and twelve hours there were practically no convulsions, but the animal was still comatose. At one hundred and twenty-four hours the animal was commencing to regain consciousness. It was still being forcibly fed. At one hundred and thirty-six hours it attempted to stand. With careful feeding and the warmth of a hot pad the animal gradually recovered from the insulin coma. There was marked spasticity of the posterior extremities, and this persisted as a permanent result. It was finally discovered that the dog was totally blind, and there was no evidence of function of the olfactory nerve. Food placed in the mouth was swallowed, and if the nose was rubbed in it it would be taken and swallowed. Nonedible material, however, was taken just as readily. During the ensuing three weeks there was no improvement in this animal's condition.

EXPERIMENT 3.—A male collie weighing 32 Kg. was given a total of 125 units of insulin over a four day period. The dog was in coma, with a variable number of convulsions, for forty-two hours of the first three days. All of the fourth and fifth days were spent in coma, with only an occasional convulsion. Administration of dextrose was commenced, and in three days the animal reached the maximum recovery. Residual damage to the brain resulted in impaired hearing but not in total deafness. The dog had formerly been quiet and now was restless, moving about his cage incessantly. Before the insulin shock he had been docile and had liked attention. Now snarling greeted any one's approach and he could be handled only with difficulty.

EXPERIMENT 4.—A male German shepherd dog weighing 41 Kg. was kept in insulin coma, with the usual incidence of convulsions, for eighty-eight hours in five days by the use of 145 units of insulin. When it recovered it was entirely normal except for hemiplegia on the right. This persisted and showed no tendency to clear up during the following weeks.

EXPERIMENT 5.—A mongrel terrier bitch weighing 10.5 Kg. was kept in coma for almost all of three days by the use of 75 units of insulin. Convulsions were extremely numerous. After recovery there was noticeable spasticity of the posterior extremities, a peculiar twitching of the head, failure to wag the tail or show the usual friendliness when called by name and loss of most of the sight in the left eye.

All of the animals used in these experiments were killed after they had been observed for three weeks after the cessation of hypoglycemia. There was no evidence of suffering, but it seemed unwise to continue life longer, for the pathologic condition of the brain was indirectly the source of some discomfort.

Apart from the fatal effects of overdoses of protamine insulin, which Allen and Vicens [8] have emphasized, recovery with permanent cerebral pathologic conditions represents an important undesirable effect not only of accidental overdosage but of treatment of neural disease with this drug. Gellhorn [11] has pointed out not only that the nervous system

11. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System: A Basis for a Rational Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **40**:125 (July) 1938.

is influenced by hypoglycemia in a manner similar to that in which it is affected by anoxia but that hypoglycemia sensitizes the central nervous system to anoxia so far as functional effects are concerned.[12] If this is so, it should also be true of pathologic changes, and it probably is; the care of the hypoglycemic condition is doubly important, for the condition of the circulation in insulin shock is frequently contributory to a state of anoxia. It is possible that administration of oxygen as well as injections of dextrose would be desirable in cases of serious overdosage with insulin. We plan to examine this point experimentally.

## SUMMARY

Overdosage with protamine zinc insulin produced the characteristic coma and convulsions in the rat. If the duration of the insulin shock was not short, the administration of dextrose in amounts sufficient to raise the blood sugar level to a normal value was without influence. Death from respiratory failure always ensued, and there was usually marked edema of the lungs.

The administration of strong solutions of dextrose by stomach tube to rats or dogs or intraperitoneally to rats which have been in insulin shock for some time is frequently followed by convulsions and sudden death. Administration of water occasionally has the same effect. These results are probably due to a sudden electrolyte shift and changes in the concentration of the body fluids superimposed on an impaired general circulation and cerebral stasis and to degenerative changes consequent on the preceding hypoglycemia.

Hypoglycemia is known to affect the metabolism of the brain in an adverse manner and to give rise to degenerative changes. We found evidence that prolonged hypoglycemia led to permanent functional damage to the brain. After long periods of hypoglycemia due to the administration of protamine zinc insulin over a period of three to five days, permanent sensory and motor disturbances ensued. The dogs had impairment or complete lack of vision or hearing, disturbances of the emotional complex, incoordination, spasticity and even paralyses.

These results show once more the necessity for great care in preventing unnecessary hypoglycemia. The administration of insulin should be carefully controlled. The shock should be maintained for as short a time as possible when it is produced for therapeutic purposes.

12. Gellhorn, E.; Ingraham, R. C., and Moldavsky, L.: The Influence of Hypoglycemia on the Sensitivity of the Central Nervous System to Oxygen Want, J. Neurophysiol. **1**:301, 1938.

Eli Lilly and Company supplied the protamine zinc insulin used in the early part of this study. Additional supplies were furnished by E. R. Squibb & Sons.

# TRANSPORT OF AIR ALONG SHEATHS OF PULMONIC BLOOD VESSELS FROM ALVEOLI TO MEDIASTINUM

## CLINICAL IMPLICATIONS

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## EXPERIMENTAL INVESTIGATIONS

*Pulmonic Interstitial Emphysema.*—That air, after it has broken from the pulmonic alveoli into the interstitial tissue of the lung, can travel along the sheaths of the pulmonary blood vessels, in artificial channels which it dissects for itself, to the root of the lung, and from there into the mediastinum, has been amply demonstrated in a series of experiments on cats and other animals.[1] The alveoli are made to leak by overinflating them, and so stretching and straining the walls. This is accomplished by passing a truncated catheter into a region of the lung (the lower lobe of the right lung is conveniently used) and blowing air into it, thus extending the alveolar walls and producing many small ruptures in their floors, which overlie the small branches of the pulmonary blood vessels. It is important to visualize clearly this locus of the leakage,[2] the area of which varies in size depending on the volume of lung thus hyperinflated. Continuance of the blast means persistence of the air leakage and onward movement of the air through these artificial tunnels in the vascular sheath, which increase in size as they are followed toward the root of the lung.

Air bubbles in the pulmonic arterial and venous sheaths may easily be seen with the naked eye at the roots of the lungs in the freshly opened thorax. By careful inspection and probing the situation of the air in the vascular sheaths can be demonstrated. By slicing the fresh lung the bubbles can be seen, but with greater difficulty, and then only in the region of the hilus in the animal lungs. It is not easy to determine their exact relation to the blood vessels under these conditions, for the

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1. Pulmonic perivascular emphysema so induced has been studied intensively in material from 12 cats. In addition, 23 other animals (14 cats and 9 rabbits) have been experimented on to clear up special points.

2. Macklin, C. C.: Pneumothorax with Massive Collapse from Experimental Local Over-Inflation of the Lung Substance, Canad. M. A. J. **36**:414, 1937.

air diffuses out quickly, and the operation of slicing, even when carefully done with a sharp knife, disturbs its relations, and even leads to its evacuation. Thus it is necessary to rely on properly fixed material.

We have found that fixation is best accomplished by removing the collapsed lungs from the animal immediately after the experiment and filling them by way of the bronchial tree with a fixative (40 per cent solution of formaldehyde diluted 1:10, Zenker's fluid and others were used). The lungs were then immersed in the same fluid and allowed to stand for a day or two, until well hardened. Thin sections were cut from various parts, extending from the region of overdistention to the root of the lung. Blocks 2 mm. or more in thickness were cut transversely or longitudinally to the long axis of the pulmonary blood vessels and examined with the binocular microscope; these were very instructive, for in a series of such pieces it was possible to trace the track of the air from the sheaths of the finer vessels, which had been invaded, down the vascular tree to the large sheaths of the pulmonic vascular stems at the roots. In these fixed tissues the air has, of course, diffused out, but the pattern of the bubbles remains. It often is found that the vessel is obviously encroached on by the bubbles, and may even be completely collapsed by the pneumatic armature. In figure 1 the arterial and venous branches seen are each separated from the environing lung tissue by a thick zone of air. The former loose, succulent connective tissue of the sheath has been greatly distended; indeed, little or nothing is seen of this original tissue but thin strands joining the lung substance with the wall of the vessel. The blood flow in such a part must be almost, if not completely, stopped. In figure 2 the invasion of air is of more moderate degree, but even here it is plain that the air would impose a circulatory handicap. The most striking accumulations are in the roots of the lungs where the converged air streams have merged into large blebs. Here the air block is of strategically greater importance than it is more peripherally, for it impinges on main trunks rather than on smaller branches. The end result would obviously be a serious impediment to the pulmonary circulation. In experimental animals I have never observed the air in the sheaths of the bronchi nor in those of the bronchial blood vessels. Thus pulmonic interstitial emphysema is primarily an affair of the sheaths of the pulmonic blood vessels. There are, particularly in the region of the hilus in larger lungs, extensions of air into contiguous connective tissue formations, but in this experimental material pulmonic interstitial emphysema was practically synonymous with pulmonic perivascular emphysema.

*Pneumomediastinum.*—Further leakage into the peripheral interstitium of the lung may cause the three dimensional air river to break through into the mediastinum, and so the tissues here are distended with large blebs. The pressure may become so great that escapes must be

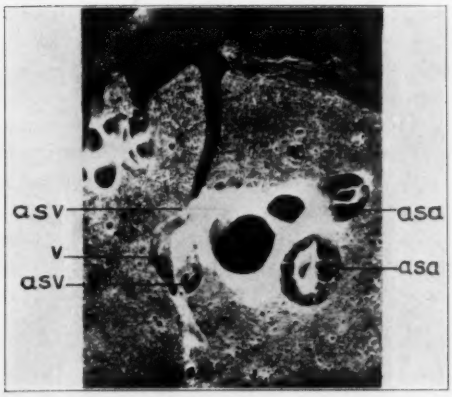


Fig. 1.—Photomicrograph (× 2.8) of a thick transverse, freehand slice through the region of the hilus of the lower lobe of the right lung of a cat which had been subjected, while alive and under anesthesia induced with ether and dial (2 cc. injected intraperitoneally), to hyperinflation with pure air blown in through a catheter inserted by way of an opening in the trachea, just below the larynx. The pressure was 2 cm. of mercury at the beginning and was increased 2 cm. each minute for a total of six minutes of continuous insufflation until a maximum of 12 cm. of mercury was attained. The insufflation was pressed until the animal's chest and abdomen were well distended.

The bronchus has been cut at a fork. The main stem of the bronchus is the large rounded, dark spot near the center of the field; its branch is the smaller rounded spot to the right and above. No air is seen in the bronchial sheaths. Two branches of the pulmonary artery are seen—one to the right of the main bronchus and one to the right of the branch. Each is entirely surrounded by an air space, *asa*. The cobweb-like formation of connective tissue, representing the strands that remain to connect the wall of the artery with the outer boundary of the vascular sheath, is well seen around the larger arterial branch. The pulmonary vein (*v*) is seen to the left of the main bronchus. It has been cut obliquely and is not as plainly shown as are the arteries. Around it is the air space *asv*.

This is a good example of a case of marked pulmonary vascular interstitial emphysema induced experimentally by prolonged local overinflation of a region of the lung, as seen around the larger blood vessels of the hilus, under low power. There was double pneumothorax in this case, with complete massive collapse. Immediately after the massive collapse occurred, the lungs were carefully removed and filled with Bouin's fluid, by means of a cannula in the trachea, to the degree of normal inflation. They were sectioned after hardening in this fluid.

The lumens of arteries and veins have been almost obliterated by the pressure of the air in the sheaths, so that the blood flow must have been almost completely stopped. Air in the mediastinum and retroperitoneum added to the circulatory impediment.

found; I have met air freshets breaking through downward—into the retroperitoneal space (with even further onflow into the groin and leg); upward into the root of the neck, face, axilla, wall of the chest and arm; forward between the parietal pleura and the pericardium, to appear as blebs overlying the heart (pneumoprecordium), and laterally into the opposite lung or unbloated parts of the same lung. Of course, the air in the mediastinum and contiguous regions interferes further with the function of the vascular system. The heart and great vessels are pressed on, it may be grievously. Ballon and Francis [3] induced a fall in blood pressure in animals by increasing the intramediastinal pressure. The coronary vessels must be compressed in marked cases, and it seems likely that the current within them is slowed. Embarrassment occurs similarly in all other blood vessels which are implicated in the spread of the emphysema, but it must be in minor degree where the region is unconfined and the environing pressure not greatly raised. The most important blockade is in the mediastinum and lung. In my experimental animals there was, in extreme cases, such obstruction that the circulation was stopped. As an incident in the course of experimental pneumomediastinum we observed pneumothorax, and in the cases investigated it was caused by rupture of the mediastinal wall, strained past endurance.[2] Its effect is to relieve the pressure in the mediastinum and lung, thus freeing the circulation; at the same time, by collapsing the lung, it stops the further leaking of air into the vascular sheaths. Unfortunately, in these animals it was always double and complete, and hence was incompatible with continuance of life.

## CLINICAL PARALLELS

There are clinical parallels for this condition of pulmonogenic pneumatization of the interstitial tissues, and for all aspects of it, particularly pulmonary interstitial emphysema and pneumomediastinum. Contributions to the literature have recently been numerous.

*Pulmonic Interstitial Emphysema.*—This condition in man, as in animals, is fundamentally emphysema of the vascular sheaths. True, there are often extensions from these sheaths into the adjoining connective tissue, and the air sometimes dissects along a trabecula of connective tissue to the pleura, to form a bleb under it, particularly in the region of the root. It is possible that these blebs rupture at times, to cause pneumothorax, as some authors have stated. I have seen an excellent example of air canalization of the sheaths of the pulmonic vessels in a human lung which had been properly fixed. The reason

3. Ballon, H. C., and Francis, B. F.: Consequences of Variations in Mediastinal Pressure: Mediastinal and Subcutaneous Emphysema, Arch. Surg. **19**:1627 (Dec., pt. 2) 1929.

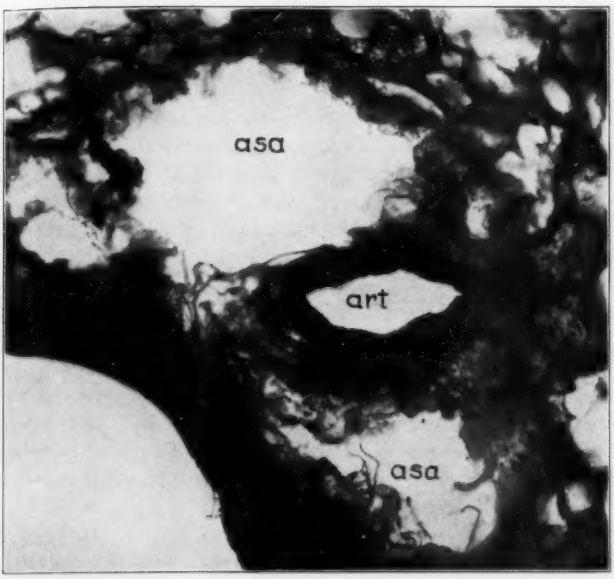


Fig. 2.—Photomicrograph of a thick frozen section, stained with the Mallory technic. Magnification, × 86. This tissue was from the lower lobe of the right lung of a full-grown cat which had been subjected, while alive and under anesthesia induced with ether, to insufflation of air charged with osmic acid vapor, introduced via a catheter, for a period of twelve minutes. The catheter tip was observed at autopsy in the main bronchus of the lower lobe of the right lung. There were double pneumothorax and massive collapse. The lungs were removed one-half hour after death and filled, by way of the trachea, with Orth's fluid to the extent of ordinary inflation. Frozen sections were cut after the material was hardened. The osmic acid vapor had nothing primarily to do with the perivascular interstitial emphysema.

Near the center of the field is seen a contracted branch of the pulmonary artery, *art.* Above and below it are artificial air spaces, *asa.* In the fresh condition the presence of air bubbles makes these spaces smooth in contour, but the air has been replaced by the reagents used and the walls of the spaces appear ragged. Part of a bronchial wall is seen in the lower left corner. The average diameter of this branch of the pulmonary artery, in the fixed and dehydrated condition, is about 0.3 mm. This is a good example of invasion of air and canalization of the sheaths of the smaller branches of the pulmonary artery. The presence of the air diminishes the caliber of the blood vessel and impedes the circulation.

that so little has been known about the exact location of air in the interstitium of the human lung is because (1) fixation has been delayed until much, or indeed all, of the air has diffused out, and (2) fixation has been by immersion of the excised contracted pieces, from which the air has escaped. Further research by better methods is needed on the histopathologic changes induced by aberrant air in the human pulmonic interstitium. Fixation should be immediately after death, and by injection into the bronchial tree.

Cases of pure pulmonic interstitial emphysema have not been well differentiated clinically. Roentgenographic demonstration is not easy. The condition is often so complicated by pneumomediastinum and its sequelae that it is difficult to isolate cases symptomatically. Even when the air has not diffused beyond the lung there is undoubtedly an impediment to the circulation, and the degree of this would depend on several factors, among them the extent of the area of leakage. The fact, however, that in the lungs the largest air blebs gather at the root, where they compress the greater vessels and can do most damage, makes a small area of leakage assume an importance out of all proportion to its size. The sheaths are apparently able to stretch to a considerable degree, to make room for the invading air, but when they are well pneumatized, as I have seen them, the vessels are collapsed and appear to be clamped, as it were, in an air vise.

Do this pressure and interference with the flow elicit pain, particularly from the obstructed arteries? This question has been raised,[4] but as yet there is no answer. Certainly there are many cases in which pain in the lateral portion of the chest ushers in the outspoken signs and symptoms of pneumomediastinum. Hamman,[5] Morey and Sosman,[6] Phillips,[7] Maxwell [8] and many others mentioned lateral pain. Sometimes it is sharp; sometimes it is described as a "stitch" in the side. Between the time of onset of the lateral pain and that of the precordial pain of pneumomediastinum there is often an interval such as would presumably allow for the transit of the air from the vascular sheaths into the mediastinum.

Thus, the most important point about pulmonic interstitial emphysema seems to be the associated circulatory embarrassment. It must

4. Macklin, C. C.: Spontaneous Mediastinal Emphysema: A Review and Comment, M. Rec. **150**:5, 1939.

5. Hamman, L.: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. **64**:1, 1939.

6. Morey, J. B., and Sosman, M. C.: Spontaneous Mediastinal Emphysema, Radiology **32**:19, 1939.

7. Phillips, P.: Subcutaneous Emphysema During Labour, Brit. M. J. **1**:54, 1938.

8. Maxwell, J.: Spontaneous Haemopneumothorax, Brit. M. J. **1**:778, 1938.

not be forgotten, too, that infections may travel from the alveoli along these "false" channels, so starting inflammatory foci on the course of the blood vessels and in the mediastinum. Imperatori [9] mentioned such a case.

*Pneumomediastinum.*—Although pneumomediastinum has been recognized clinically for a long time, there has been a recent revival of interest in it, and some important points have been emphasized. One of these is the curious crunching sound which is heard over the region of the heart in some cases, and which, on account of the prominence given to it by Hamman,[5] may be known as Hamman's sign. This noise was attributed by Hamman, and I think with good reason, to the presence of air between the anterior parietal pericardium and the thoracic cage. I have noted frequently in my experimental animals that, on removal of the sternum and costal cartilages, a froth of bubbles of different sizes, overlying the parietal pericardium, was conspicuous. These bubbles had evidently worked themselves forward from the posterior part of the mediastinum. Agitation of them by the heart's action gives rise to the characteristic sound, which Hamman stated may sometimes be heard with the unaided ear. I have never observed air bubbles within the pericardial cavity in animals. No doubt there are many cases in which the air does not extend forward around the heart, and then there would be pneumomediastinum without the crunching sound. In these cases Hamman said that the roentgenographic evidence of air in the mediastinum may be decisive. Thus the absence of Hamman's sign does not rule out emphysema of the mediastinum. In the usual posteroanterior or anteroposterior projections it is only the more outlying pockets of air that can be seen. Lateral and oblique [10] projections should also be used. There are certainly many degrees of invasion of air, from a few small bubbles in the posterior portion of the mediastinum to the extreme inflations with eruptions into contiguous territory, as already described, and with rupture of the wall into the pleural cavity.

The pain of pneumomediastinum has often been emphasized. It seems to depend largely on the amount of distention, and has been described as sharp and stabbing.[5] It is in the precordial area. In cases in which the initial pain is lateral I suspect that it originates in the pulmonic interstitial tissue or pleura rather than in the mediastinum. The nature of the pain and its line of irradiation, sometimes down the left

9. Imperatori, C. J.: Pericarditis as a Terminal Lesion in Mediastinitis: Report of a Case Following Inhalation of a Foreign Body in the Bronchus and Accompanied by Spontaneous Emphysema, Ann. Otol., Rhin. & Laryng. **42**:923, 1933.

10. Andrus, P. M.: A New Method for the Radiographic Exploration of the Mediastinum and Concealed Portions of the Pulmonic Fields, Radiology **23**: 97, 1934.

arm, have led to the erroneous diagnosis of coronary occlusion. It is possible that the thrust of the air even through both layers of pericardium may indent the coronary blood vessels and so cause anginoid pain. The peculiar crunching noise has doubtless been taken for a pericardial rub. Thus, on account of mediastinal emphysema, unfavorable prognoses have been made baselessly.[11]

It is remarkable how speedily the air is absorbed from the mediastinum when its inlet is stopped and proper therapeutic measures are taken. One to two weeks, with appropriate treatment, is usually sufficient for its disappearance. Noteworthy, too, is the extent of the spread of air that may occur without entailing a really critical condition. The neck, face, chest and other parts of the patient may look severely bloated; yet he may soon regain his normal appearance. Sometimes, however, the area of pulmonic leakage is extensive, with copious infiltration of the vascular sheaths, as, for instance, in cases of bronchial impaction by foreign bodies in which a main stem is occluded, leading to serious diminution in lung volume through absorption of the air. Here the compensatory alveolar ectasia may be voluminous and of a severe type. The leaking area may be on the same side as the atelectasis, or it may be in the opposite lung, or in both. When the interstitial air pressure in the lungs and mediastinum embarrasses the circulation markedly there are dyspnea, cyanosis and dilatation of the right side of the heart. Pneumothorax, intervening by rupture of the mediastinal wall, as in my experimental animals, and possibly also in man, or by rupture of a subpleural bleb in the region of the root, connected, as already described, with the air-inflated vascular sheaths, relieves the impediment to the circulation and stops the leak by overcoming its cause, the hyperinflation. It may thus be regarded as a natural therapeutic method. It is often slight in degree,[5] and does not always occur spontaneously in these cases. If the patient is in a critical condition it may be necessary to remove the air. The root of the neck may be incised and the air drawn off with a suction apparatus (Tiegel[12]). A hard rubber catheter may be inserted from the root of the neck into the mediastinum, or the surgical method of Furstenberg and Yglesias[13] may be used. Artificial pneumothorax on the side of the leak is likely to put an end to further transport of air and invasion of the mediastinum by correcting the overinflation which lies at the basis of the leaking.

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11. Hamman, L.: Spontaneous Interstitial Emphysema of the Lungs, Tr. A. Am. Physicians **52**:311, 1937.

12. Tiegel, M.: Ein einfaches Verfahren zur Bekämpfung des mediastinal Emphysems, Zentralbl. f. Chir. **38**:420, 1911.

13. Furstenberg, A. C., and Yglesias, L.: Mediastinitis: A Clinical Study with Practical Anatomic Consideration of the Neck and Mediastinum, Arch. Otolaryng. **25**:539 (May) 1937.

*Mode of Air Leakage.*—A few further details as to the mechanics of leakage of air from the alveoli may here be in order. The aberrant air, as has been seen, enters the vascular sheaths through numerous minute openings in the floors of the alveoli which overlie the finer ramifications of the pulmonary arteries and veins. These ruptures, which are situated in the meshes of the capillaries, are brought about by (*a*) undue stretching and weakening of these alveolar bases during overdistention of the part with air, and (*b*) a pressure gradient from alveolus to vascular sheath. The gradient is a direct result of the overdistention, which has the effect of pulling away the enveloping alveoli from the pulmonic blood vessels, and so of diminishing the pressure in the sheaths around them.

The sites of the ruptures may be indicated by the injection of hot gelatin containing particles of carmine of small size into the bronchial tree of a collapsed lobe which has immediately before been forced to leak air by experimental overinflation.[14] This zone of overinflation in the animals lay immediately around the tip of the catheter from which the air issued. The pressure registered on the mercury manometer during the insufflation, from 1 to 22 cm. of mercury, was somewhat higher than that to which the alveoli were actually exposed, for there was some reflux, due to the fact that the tip of the catheter was loosely inserted. In sections cut from this material, properly fixed, the carmine particles appeared in small heaps on the air side of the alveolar wall, where they had been filtered out as the fluid gelatin passed through the minute ruptures into the underlying vascular sheaths. Where the ruptures were larger the carmine appeared in streams of particles leading from the sites of rupture into the mass of gelatin in the sheath, which had displaced, in part at least, the air which had invaded it but a short time before, during the first stage of the experiment. I have seen no cases of a single ruptured alveolus, such as have been said by some authors to be implicated possibly in such leakages.

*Dangers from Atelectasis.*—In the experimental cases the region of enlarged volume, or alveolar ectasia, was centrally situated, around the tip of the catheter. It was ballooned by the blast of air. Around this focus was a zone where the air spaces must have been reduced in volume, to compensate for the central enlargement. But in cases in man, on the contrary, it is often the area of diminished volume, or atelectasis, which is centrally placed, while around it, or adjoining it, there is compensatory expansion of the air spaces, or, as it is often called, com-

14. Macklin, C. C.: The Site of Air Leakage from the Lung Alveoli into the Interstitial Tissue During Local Over-Inflation in the Cat, Anat. Anz. **85**:78, 1938.

pensatory emphysema.[15] It is doubtless from this hyperexpanded region that the leakage of air occurs. The importance of diminution in lung volume from any cause should therefore be stressed, for if the capacity of the thorax cannot be lessened to cover the reduction, there must necessarily be an expansion of lung substance to fill the space.

Atelectasis thus assumes a baneful significance, for it engenders overstretching of the neighboring alveoli, with attendant danger of multiple rupture. The literature is full of instances of pulmonic interstitial emphysema associated with bronchopneumonia. A number of cases were reported during the great influenza epidemic of 1918, as those by Kelman [16] and Clark and Synnott.[17] Thus, bronchopneumonia may be the basis of air leakage. The influences of inflammation and toxemia probably weaken the alveolar bases, so increasing the likelihood of rupture. In some of these cases atelectasis is insidious; yet even in cases in which no trace of it has been found I suspect its complicity.[4] More delicate technics for its detection may yet reveal reduction in pulmonic volume in all cases of interstitial emphysema of the lungs. This reduction may be large, as in some instances of impaction by foreign bodies already alluded to or in cases of massive collapse of the lungs or of lobectomy without spatial compensation. In all cases one may regard reduced volume in lung tissue as a potential cause of pulmonic interstitial emphysema.

In the usual cases of pulmonic interstitial emphysema and pneumomediastinum in man there is no preceding insufflation of air, as in the experimental animals, but there must be a descending pressure gradient from the area of alveolar ectasia to the tissue fluid spaces of the pulmonic vascular sheaths of the region. The transport of air along the vascular sheaths is doubtless much slower and less spectacular than it is when air is actually being blown in. Coughing probably facilitates the leakage. It seems likely that the lengthening and shortening movements of the pulmonic blood vessels, associated with similar movements of the bronchi in respiration, serve to move the train of bubbles along through the vascular sheaths. The danger of atelectasis from this angle should be

15. It would be desirable if pathologists and clinicians could establish a better nomenclature for the conditions known as "emphysema." This term is used for a simple distended state of the alveoli, as in "compensatory emphysema"; for a degenerate condition of the alveolar walls associated with increased volume, as in "pulmonary emphysema," or "pulmonic parenchymatous emphysema," and for the totally different condition of air in the interstitial tissues, "interstitial emphysema." This application to more than one entity leads to much confusion.

16. Kelman, S. R.: Experimental Emphysema, Arch. Int. Med. **24**:332 (Sept.) 1919.

17. Clark, E., and Synnott, M. J.: Influenza-Pneumonia Cases Showing Gas in Fascial Tissues, Am. J. M. Sc. **157**:219, 1919.

kept in mind by the clinician and measures taken to correct the condition of overinflation resulting therefrom, so that the leaking may be stopped. Among the recent reports is that of Graebner,[18] who cited 3 cases in which air was demonstrated roentgenoscopically in the mediastinum. All the patients had acute obstructive laryngitis. One (7 years of age) had measles and pertussis; another (aged 16 years) had sore throat, a temperature of 104.8 F. and evidence of infectious involvement of the lower part of the respiratory tract, and the third (aged 2½ years) showed signs indicative of marked bronchopneumonia, with a temperature of 105.2 F. Graebner postulated that the air reached the mediastinum from the pulmonic interstitial tissue. It seems evident that the ability of the alveoli to retain air was impaired, and that this was due to one or more of the following factors: obstructive laryngitis, possible atelectasis and weakening of the alveolar walls following the probable overstretching and effects of the infection. Escudero and Adams[19] reported an interesting series of 9 cases of experimental spontaneous pneumothorax in dogs associated with massive collapse, and they added a single case of a similar condition in an 8 year old girl.

In some cases of pneumomediastinum and its sequelae in man, however, the mode of production is much like that in my experimental animals. Eisen[20] recently recorded a case of surgical emphysema, pneumothorax and pneumoperitoneum in a normal boy of 4 years, who, while being anesthetized with ether by the "closed" method, showed rapid pulse and respirations and evident generalized subcutaneous emphysema. The pressure of the ether vapor, passing through nasal catheters into the nasopharynx, was probably too high. Roentgenograms showed large amounts of air in the mediastinum, root of the neck and retroperitoneal tissues; there was some in the thighs and left pleural cavity. Eisen expressed the view that this air leaked out from the overinflated lung along the vascular sheaths to the mediastinum, in the way that I have described.[2] In such a case the generalized emphysema comes on rapidly, as in the experimental animals.

When one reflects on the matter, it seems marvelous that the alveoli are so perfectly air competent; the wonder is that they do not allow air to escape into the interstitial tissues more frequently. It seems, however, as though some persons are constitutionally liable to air leakage and suffer repeated attacks. Recurrent seizures of spontaneous

18. Graebner, H.: Pneumopericardium and Pneumomediastinum in Cases of Acute Obstructive Laryngitis, Arch. Otolaryng. **29**:446 (March) 1939.

19. Escudero, L., and Adams, W. E.: Spontaneous Pneumothorax Associated with Massive Atelectasis: An Experimental and Clinical Study, Arch. Int. Med. **63**:29 (Jan.) 1939.

20. Eisen, D.: Surgical Emphysema, Pneumothorax and Pneumoperitoneum: A Roentgenographic Study of a Case, Radiology **31**:623, 1938.

pneumothorax, such as Hamman [6] recorded in his case 4, seem to me to be sequelae of such leakages. It may be possible, too, that the propensity to pulmonic air leakage is hereditary, since a number of cases have been reported in which more than one member of a family has been affected, and in which there was no obvious disease to explain the leakage.[21]

This is not the place to expatiate on the occasionally fatal ending in cases of mediastinal emphysema, but the literature contains a number of such instances. The importance of the roundabout route of air transit from the alveoli to the mediastinum along the vascular sheaths grows in the mind of the reader of these reports. Leveuf and Kohn [22] reported a case of mediastinal and subcutaneous emphysema in a child of 2½ years in whom release of the air through an incision at the base of the sternum led to a prompt and permanent recovery.

## SUMMARY

1. Air may break through from overdistended alveoli of the lung into the underlying pulmonic perivascular sheaths and travel along these sheaths in channels which it makes to the mediastinum.

2. In so doing it presses on the pulmonic blood vessels and interferes with the flow of blood in the part, not only of the incoming arterial but also of the venous blood.

3. Because the air which has invaded the interstitial tissue from a local part crowds into the sheaths of the larger blood vessels at the root of the lung, its obstructive effect becomes more general, creating an impediment to the pulmonic blood flow over a wide area. The blockade of the pulmonary blood stream may have serious consequences.

4. This method of transport of air from alveoli to mediastinum along the vascular sheaths has been demonstrated convincingly in experimental animals in which air was blown through a urethral catheter into a local part of the lungs. The evidence is from fresh lungs of these animals, particularly from properly fixed and sectioned material taken from them. The same air-tunneled vascular sheaths have been noted in the human lung.

5. Clinically this transport of air and resultant circulatory impediment may occur when a region of alveolar overdistention arises. The common cause is local diminution in volume of lung substance. This reduction in volume may be relatively small, as in the common type of atelectasis, and may be multiple. Or it may be large, as in massive collapse or surgical removal of a lobe without operative compensatory

21. Gøtzsche, C.: Spontaneous Pneumothorax: Five Cases in the Same Family, Ugesk. f. læger **95**:765, 1933.

22. Leveuf, J., and Kohn, R.: Emphysème sous-cutané et médiastinal spontane chez l'enfant, Arch. de méd. d. enf. **41**:156, 1938.

spatial reduction. The leakage of air into the vascular sheaths may be prolonged over some time, with corresponding continuation of the transport of air and its evils.

6. The pneumatization of the pulmonic vascular sheaths can occur in the human subject by the development of too high an intrapulmonic pressure during the faulty administration of an anesthetic by the closed method.

7. The actual inlets for air to the sheath system are multiple and very small ruptures in the alveolar bases which overlie the finer ramifications of the pulmonary blood vessels. These openings are in the meshes between the capillaries. The alveoli so perforated are probably numerous and distributed over a comparatively wide area. No examples of grossly torn or ruptured alveoli were seen in the experimental animals.

8. Infections may similarly travel through the pulmonary interstitial tissue along the air-hollowed vascular sheaths, and give rise to infective foci along the way.

9. The only pulmonic interstitial emphysema which I have seen is that of the pulmonic blood vessels and extensions therefrom, such as those into the partitions of interstitial tissue which separate subdivisions of lung substance. In the light of this study, pulmonic interstitial emphysema becomes important because of (*a*) embarrassment to the pulmonary circulation; (*b*) spread of infection and (*c*) formation of subpleural blebs which extend from the sheaths along connective tissue trabeculae or partitions, and which may rupture and give rise to pneumothorax, as some writers have asserted. I have not yet observed such ruptured blebs, however.

10. This pathologic transport of air is dangerous also because it distends the mediastinum, so bringing further embarrassment to the circulation through pressure on the heart and great vessels. This may be fatal. Pneumomediastinum leads also to pneumoprecordium, with Hamman's sign; to interstitial emphysema of the opposite lung and hitherto unaffected regions of the same lung; to pneumoretroperitoneum (and even pneumoperitoneum) and extensions of emphysema to the groin and leg, and to emphysema of the connective tissues of the neck, head, arm, chest and abdomen. These extensions from the mediastinum have a salutary feature, inasmuch as they relieve the distress of the circulation within the mediastinum. Abatement of mediastinal pressure results also when the mediastinal wall ruptures, giving rise to pneumothorax. This also has the effect of closing the leaks.

11. Though in many clinical cases of generalized interstitial emphysema originating in this way from pulmonic leaks the condition clears up of itself in a week or two, there seem to be cases in which operative

intervention may be required for (*a*) relief of mediastinal and intrapulmonic pressure, which may threaten life through interference with the circulation, and (*b*) stoppage of the leaks. The first is accomplished by mediastinotomy and suction; the second, by artificial pneumothorax.

12. There seems to be a group of people who are constitutionally prone to leakage of air of this type from the lung. Susceptible persons may have repeated attacks. The same applies to spontaneous pneumothorax, which seems to be causally associated.

The brief list of references in this article contains only articles which have been specially selected to illustrate outstanding points. The literature pertaining to the various aspects of emphysema in the mediastinum and related parts is enormous and is growing rapidly. Many of the citations made here contain bibliographies. Treatises, such as that of Graham, Singer and Ballon (Surgical Diseases of the Chest, Philadelphia, Lea & Febiger, 1935), contain ample lists of references.

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# STUDIES ON "ESSENTIAL" HYPERTENSION

## I. CLASSIFICATION

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Arterial hypertension [1] is a common phenomenon. In some instances it is associated with diseases already plentifully described and believed to cause it. Such conditions comprise disturbances of four main systems: the genitourinary, the nervous, the endocrine and the vascular. It is generally believed that when disorders of these systems are accompanied by arterial hypertension the hypertension is a dependent phenomenon, for when they are relieved it often disappears. Such varieties of secondary arterial hypertension (*B*, table 1) are present in only a small number of all cases in which diastolic pressure is elevated. When none of these diseases is present and arterial pressure is elevated, an independent disease called "essential" (or "idiopathic") hypertension is regarded as responsible for the pathologic processes observed. Although the expression is an admission of ignorance, it must be understood that the condition called "essential" hypertension is present in over 85 per cent of all cases in which blood pressure is elevated.[2]

"Essential" hypertension itself has been regarded as a syndrome for which any one of a number of different diseases may be responsible. Fishberg [3] stated:

> It seems highly probable, in fact almost certain, that essential hypertension is merely a collective concept—for a number of conditions having in common the

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1. When the term "arterial hypertension" is used in this study it is intended to mean elevation of both systolic and diastolic pressures.

2. (*a*) Keith, M. M.: Classification of Hypertension and Clinical Differentiation of the Malignant Type, Am. Heart J. **2**:597 (Aug.) 1927. (*b*) Adson, A. W., and Allen, E. V.: Essential Hypertension: I. General Considerations, Proc. Staff Meet., Mayo Clin. **12**:1 (Jan. 6) 1937.

3. Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

positive characteristic of arterial hypertension and the negative one of the absence of primary renal disease.

An attempt at classifying cases of "essential" hypertension is one method of testing the value of this idea. The condition has been treated nosologically a number of times, usually from the point of view of its severity, its rate of progress or the state at which the process has arrived.[2] Kahler [4] attempted a physiologic analysis.

The classification now proposed for cases of "essential" hypertension is the outgrowth of the observation that the wide variety of clinical disturbances associated with this condition can, for the most part, be divided into the same four groups (*C*, table 1)—renal, neurogenic, endocrine and vascular—as the diseases to which arterial hypertension is commonly thought to be secondary. Further evidence for the soundness of this grouping of cases of "essential" hypertension is the fact that an elevation of arterial pressure can be produced experimentally in animals by disturbance of one or other of at least three of these same four systems (*A*, table 1)—the urinary, the nervous and the vascular. It is not yet certain whether it can be brought about by disturbance of the endocrine system. The mechanisms of the three types of disturbances are still imperfectly understood, but it is important that in many respects they appear analogous to those of similar disturbances in human beings. The classification is, for these reasons, physiologic.

Neither lesions resulting from prolonged arterial hypertension (as indicated in cardiac failure, renal failure or apoplexy) nor symptoms and signs believed to be dependent on hypertension (palpitation or headache) have been used as a basis for classification, although occurrence of these symptoms and signs has been used to distinguish the various groups in point of behavior.

In making this classification, 218 cases of "essential" hypertension studied in this hospital during the past ten years were reviewed. At the time of writing, 90 of the patients are dead; of 11 there is no information, and 117 are living. The progress of 114 continues to be studied. All were referred as having typical "essential" hypertension and either exhibit or have exhibited elevation of diastolic pressure without failure of renal function. In most cases the time of the onset of hypertension is known within two years.

4. Kahler, H.: Die Blutdrucksteigerung, ihre Entstehung und ihr Mechanismus, Ergebn. d. inn. Med. u. Kinderh. **25**:265, 1924.

TABLE 1.—*Analysis of Arterial Hypertension (Elevation of Diastolic Pressure) According to the Four Systems Affected by the Associated Disturbances*

| I<br>Renal Parenchyma | II<br>Nervous System | III<br>Endocrine System | IV<br>Arterial Vascular System |
|---|---|---|---|
| **A. Experimental Lesions Resulting in Hypertension in Animals** | | | |
| Roentgen sclerosis of kidneys [a]<br>Chemical nephritides (oxalate) [b]<br>Serum nephritis [c]<br>Reduction of renal substance [d]<br>Constriction of renal vein [e]<br>Ureteral ligation [f] | Removal of carotid sinus and aortic depressor nerves [g]<br>Intracisternal injection of kaolin [h]<br>Hypothalamic injury [i]<br>Increased intracranial pressure [j] | Injections of estrogen and pitressin (beta hypophamine) resulting in renal lesions like those found in eclampsia (blood pressure not stated) [k] | Partial constriction of renal artery [e]<br>High intake of vitamin D and cholesterol [m] |
| **B. Lesions Associated with Hypertension in Man (partly after Fishberg)** | | | |
| Renal diseases with renal failure<br>Glomerulonephritis (especially chronic)<br>Urinary obstruction<br>Polycystic kidneys<br>Necrotizing nephroses<br>Suppurative nephritis (rare)<br>Pyelonephritis | Tumors of brain, etc., giving rise to increased intracranial pressure<br>Diseases of the brain stem (bulbar poliomyelitis, etc.) | Pituitary basophilism<br>Tumors of adrenal glands<br>Tumors of ovary (arrhenoblastoma)<br>Ovarian hypofunction (?) | Obstructive arteriosclerosis of renal artery [n]<br>Periarteritis nodosa of renal artery<br>Coarctation of aorta [o]<br>Lead poisoning |
| **C. Clinical Phenomena Associated with So-Called Essential Hypertension** | | | |
| Renal Diseases without renal failure or antedating hypertension | Diencephalic syndrome | Disturbances of the endocrine system | Arteriosclerosis |
| (Renal hypertension) | (Nervous hypertension [?]) | (Endocrine hypertension [?]) | (Arteriosclerotic hypertension [?]) |

a. Hartman, F. W.; Bolliger, A., and Doub, H. P.: Experimental Nephritis Produced by Irradiation, Am. J. M. Sc. **172**:487 (Oct.) 1926.

b. Arnott, W. M., and Kellar, R. J.: Effect of Renal Denervation on the Blood Pressure in Experimental Renal Hypertension, J. Path. & Bact. **42**:141 (Jan.) 1936.

c. Arnott, W. M.; Kellar, R. J., and Matthew, G. D.: Hypertension Associated with Experimental Serum Nephritis, Edinburgh M. J. **44**: 205 (April) 1937.

d. Chanutin, A., and Barksdale, E. E.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: Relationship of Left Ventricular Hypertrophy, Width of Cardiac Muscle Fiber and Hypertension in Rat, Arch. Int. Med. **52**: 739 (Nov.) 1933. Wood, J. E., Jr., and Ethridge, C.: Hypertension with Arteriolar and Glomerular Changes in Albino Rat Following Sub-Total Nephrectomy, Proc. Soc. Exper. Biol. & Med. **30**: 1039 (May) 1933.

e. Pedersen, A. H.: A Method for Producing Experimental Chronic Hypertension in the Rabbit, Arch. Path. **3**: 912 (May) 1927.

f. Harrison, T. R.; Mason, M. F.; Resnik, H., and Rainery, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, Tr. A. Am. Physicians **51**: 280, 1936.

g. Koch, E., and Mies, H.: Chronischer arteriellen Hochdruck infolge Dauerausschaltung der Blutdruckzügler, Krankheitsforschung **7**: 241 (July) 1929.

h. Dixon, W. E., and Heller, H.: Experimentelle Hypertonie durch Erhöhung des intrakraniellen Druckes, Arch. f. exper. Path. u. Pharmakol. **106**: 265 (June) 1932. Heller, H.: Ueber die Reizempfänglichkeit der Blutdruckzentren und die experimentelle Erzeugung zentral bedingten Hochdrucks, Klin. Wchnschr. **13**: 241 (Feb. 17) 1934.

i. Walter, C. W., and Pijoan, M. J.: Persistent Hypertension Due to Hypothalmic Injury, Surgery **1**: 282 (Feb.) 1937.

j. Cushing, H.: Concerning a Definite Regulatory Mechanism of the Vasomotor Center Which Controls Blood Pressure During Cerebral Compression, Bull. Johns Hopkins Hosp. **12**: 290 (Sept.) 1901.

k. Byrom, F. B.: Effect of Oestrogenic and Other Sex Hormones on the Response of the Rat to Vasopressin, Lancet **1**: 129 (Jan. 15) 1938.

l. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**: 347 (March) 1934.

m. Appelrot, S.: Hypervitaminosis D and Blood Pressure in Dogs, Am. J. Physiol. **105**: 294 (Aug.) 1933. Handovsky, H.: Chronic Hypertension in Dogs During the Oral Administration of Vitamin D, J. Physiol. **62**: 68 (Aug.) 1937.

n. Goldblatt, H.: Personal communication to the authors.

o. Steele, J. M., and Cohn, A. E.: The Nature of Hypertension in Coarctation of the Aorta, J. Clin. Investigation **17**: 514 (July) 1938.

The cases were divided into five main groups, as follows:

I. Renal Disease
  1. Antedating the onset of arterial hypertension
    (*a*) Symptoms or signs of organic renal disease of any nature
    (*b*) History of pathologic urinary constituents
  2. Probably antedating the onset of arterial hypertension
    (*a*) Renal abnormalities not resulting from hypertension
    (*b*) Lesions of chronic glomerulonephritis at autopsy (in a few cases)
  3. Occurring after the onset of arterial hypertension
    (*a*) Abnormal renal lesions not usually thought to be associated with or resulting from hypertension

II. Disorders of the Nervous System
  "Hypertensive diencephalic syndrome" of Page (see section II) without other classifying criteria

III. Endocrine Dysfunction
  Evidence of disturbance in the glands of internal secretion

IV. Vascular Disease
  1. Peripheral arteriosclerosis (in elderly persons) without criteria pointing to other classes
  2. Severe arteriosclerosis in persons of any age, i. e., calcification on roentgen or postmortem examination

V. Unclassified
  Conditions which cannot be classified according to any of the appearances mentioned and conditions on which data are insufficient for classification

Two hundred and eighteen cases are a small number for classification, especially when they seem, to a certain extent, selected, since the proportion in which hypertension developed before the age of 40 was extraordinarily large (68 per cent). The effort to test further the degree to which the hypertension in these cases is genuinely "essential" is nevertheless important and, we believe, rewarding. The various groups into which the cases fall will be discussed separately.

### I. ORGANIC RENAL DISEASE

In the recent literature a number of reports have appeared of cases in which arterial hypertension was associated with unilateral renal disease of various sorts. Removal of the affected kidney resulted in prolonged and dramatic decreases in arterial pressure in cases of pyelonephritis,[5] adenosarcoma (Wilms' tumor),[6] partial constriction of a renal

5. (*a*) Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889 (Nov.) 1937. (*b*) Baker, N. W., and Walters, W.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis: Treatment by Nephrectomy, Proc. Staff Meet., Mayo Clin. **13**:118 (Feb. 23) 1938.

6. Pincoffs, M. C., and Bradley, J. E.: The Association of Adenosarcoma of Kidney (Wilms' Tumor) with Arterial Hypertension, Tr. A. Am. Physicians **52**:320, 1937.

artery [7] and infarction of the kidney.[8] Also, the relation of chronic pyelonephritis [9] and other diseases of the kidney [10] to arterial hypertension has been emphasized. These reports and those indicating that a variety of experimental renal disturbances appear to cause hypertension in animals [11] have made it seem necessary to examine the state of the kidneys in our cases. Organic renal disease of any nature antedating or probably antedating the development of arterial hypertension was believed important from this point of view. Cases in which various lesions of the kidneys were observed at autopsy have also been included. There were 56 such cases (26 per cent).

The renal symptoms and signs encountered were numerous and various. There were cases (6) in which acute nephritis was followed by arterial hypertension and what was considered to be normal renal function; cases (8) in which, post mortem, lesions typical of chronic glomerulonephritis were discovered in spite of the fact that the course of the illness was indistinguishable from that of essential hypertension; cases (8) in which, before the onset of hypertension, histories of attacks of renal calculus were given; cases (4) in which pyelonephritis antedated the onset of hypertension, in 3 of which pregnancy appeared as a complication; cases (2) in which bilateral hydronephrosis was present without renal insufficiency; a case (previously reported [12]) in which severe renal damage followed excessive use of alkalis and in which, three years later, hypertension was present with normal renal function; a case in which hypertension developed after an episode of nitrogen retention and albuminuria in consequence of a severe burn from a sun lamp; cases (8) in which there was a history of persistent albuminuria antedating the onset of hypertension; cases (5) in which there was persistent pyuria, and cases (13) in which miscellaneous renal lesions were noted of a type not usually considered to result from arterial hypertension (table 2).

7. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Disease, J. Urol. **39**:611 (May) 1938.

8. Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension, J. Urol. **39**:627 (May) 1938.

9. (*a*) Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, Ann. Int. Med. **11**:149 (July) 1937. (*b*) Peters, J. P.; Lavietes, P. H., and Zimmerman, H. M.: Pyelitis in Toxemias of Pregnancy, Am. J. Obst. & Gynec. **32**:911 (Dec.) 1936. (*c*) Zimmerman, H. M., and Peters, J. P.: Pathology of Pregnancy Toxemias, J. Clin. Investigation **16**:397 (May) 1937.

10. Leiter, L.: Unusual Hypertensive Renal Disease, J. A. M. A. **111**:507 (Aug. 6) 1938.

11. A summary of the various methods employed for the production of experimental renal hypertension is given in table 1.

12. Steele, J. M.: Renal Insufficiency Developing During Prolonged Use of Alkalis: Report of a Case, J. A. M. A. **106**:2049 (June 13) 1936.

TABLE 2.—*Renal Disease*

| Case No. | Sex | Patient | Family† History | Age at Onset,§ Years | Duration,‖ Years | Symptoms¶ When First Seen | Average Extremes‡‡ of Blood Pressure, Mm. Hg | | Ocular Fundi** | | Progress†† | Present State§§ | Other Classifying Signs## | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Highest | Lowest | Arterio-sclerosis | Hemorrhage or Exudate | | | | |
| | | | | | | Acute Nephritis Before Onset | | | | | | | | |
| 1 | ♂ | J. B. | 0 | 24 | 2 | H+C | 230/150 | 220/130 | + | +++ | C-R | D-R | 0 | Acute nephritis, at 23, with malignant course |
| 2 | ♂ | J. L.* | 0 | <24 | >2 | Ce | 240/140 | 190/110 | +++ | + | C | D-C | IV+ | Same, with epilepsy |
| 3 | ♂ | J. C.* | 0 | 27 | 11 | 0 | 260/140 | 190/120 | 0 | +++ | R | D-R | IV+ | Acute nephritis, at 27, calculus at 35 |
| 4 | ♀ | A. C. | 0 | 19 | 3 | H | 190/120 | 160/110 | + | + | C-R | D-R | 0 | Acute nephritis, at 19, with malignant course |
| 5 | ♀ | D. C. | 0 | 21 | ½ | C | 250/160 | 210/140 | 0 | ++ | C-R | D-C-R | 0 | Same at 20 |
| 6 | ♀ | S. S. | 0 | 30 | 17 | 0 | 160/100 | 140/ 90 | 0 | 0 | ? | L | 0 | Scarlet fever and nephritis, at 30 |
| | | | | | | Glomerulonephritis at Autopsy | | | | | | | | |
| 7 | ♂ | R. J.† | 0 | <26 | >1 | C | 210/150 | 170/120 | 0 | +++ | C-R | D-R | IV+ | Malignant course |
| 8 | ♂ | P. M. | 0 | 22 | 2 | H | 210/130 | 170/ 80 | 0 | ++++ | R | D-R | 0 | Malignant fever |
| 9 | ♂ | G. A. | 0 | <47 | >2 | H-C | 230/140 | 180/105 | ++ | ++ | R | D-C-R | IV+ | Malignant course |
| 10 | ♂ | F. W. | 0 | 33 | 7 | 0 | 250/160 | 220/130 | + | ++ | C-R | D-R | IV++ | Renal colic (?) calculus at 39 |
| 11 | ♂ | A. B. | + | 30 | 12 | H | 250/150 | 220/140 | ++ | +++ | R | D-C-R | IV++ | |
| 12 | ♂ | E. B. | + | 41 | 2 | H-C | 260/190 | 230/120 | 0 | ++++ | C-R | D-C-R | 0 | Albuminuria, pyuria at 36 |
| 13 | ♂ | D. H. | + | 37 | 2 | H | 235/160 | 220/125 | 0 | ++++ | C-Ce | D-Ce | 0 | Albuminuria at 22-37 |
| 14 | ♀ | H. S. | 0 | 25 | 12 | H-C | 270/170 | 220/120 | + | +++ | C-R | D-C-R | IV++ | |
| | | | | | | Renal Calculus Before Onset | | | | | | | | |
| 15 | ♂ | P. M.† | 0 | 23 | 4 | H | 210/140 | 150/100 | 0 | ++ | 0 | L | II+ | Calculus removed at 23 |
| 16 | ♂ | D. W.† | ++ | 41 | 7 | H | 230/150 | 190/120 | 0 | ++++ | R | L | 0 | Calculi at 35, and later |
| 17 | ♂ | I. F. | + | 27 | 3 | H | 200/140 | 170/120 | 0 | ++ | 0 | L | II+++ | Calculus at 25, passed |
| 18 | ♂ | J. C. | 0 | 55 | 5 | 0 | 200/120 | 160/110 | + | 0 | 0 | L | 0 | Calculus removed at 45, passed at 48 |
| 19 | ♂ | M. H. | 0 | 31 | 10 | H | 210/130 | 180/125 | + | 0 | R | D-? | 0 | Calculus at 26, passed |
| 20 | ♂ | I. M. | + | <45 | >1 | 0 | 270/160 | 265/140 | + | +++ | C-R | D-C | IV++ | Calculus at 39 and 40, passed |
| 21 | ♂ | H. S. | + | 34 | 2 | H | 220/140 | 180/125 | 0 | + | C-R | D-C-R | IV+ | Calculus and infection at 22 and 34; mild bilateral hydronephrosis |
| 22 | ♂ | L. B. | + | 45 | 8 | 0 | 180/130 | 145/100 | 0 | 0 | 0 | L | IV+ | Calculi at 41 and later |
| | | | | | | Pyelonephritis | | | | | | | | |
| 23 | ♀ | H. F. | + | 24 | 8 | H | 260/140 | 220/120 | 0 | ++++ | R | D-R | 0 | With pregnancy at 21 |
| 24 | ♀ | M. F. | 0 | 29 | 7 | H-C | 300/160 | 220/130 | + | + | C-Ce | L | IV+ | With pregnancy at 18 and 24 |
| 25 | ♀ | M. P. | + | 29 | 16 | H | 260/170 | 210/150 | ± | ++ | C-R-Ce | D-C-R | IV+++ | With pregnancy at 29 |
| 26 | ♀ | A. L. | 0 | 33 | 1 | 0 | 230/150 | 210/130 | 0 | + | R | D-R | 0 | At autopsy |
| | | | | | | Miscellaneous Renal Lesions | | | | | | | | |
| 27 | ♂ | L. W. | 0 | 36 | 4 | 0 | 185/110 | 150/100 | + | 0 | R | D-R | IV+ | Congenital cystic kidney, left |
| 28 | ♂ | H. A. | 0 | <47 | >½ | C | 280/170 | 240/150 | 0 | ++++ | C-Ce | D-Ce | IV++++ | Tuberculosis of kidney, unilateral |
| 29 | ♂ | W. A. | 0 | 28 | 9 | 0 | 210/145 | 180/125 | +++ | +++ | R | D-R | IV++ | Tuberculosis of kidney, unilateral |
| 30 | ♂ | J. G. | ++ | 21 | 11 | 0 | 230/140 | 190/100 | 0 | + | 0 | D | 0 | Moderate bilateral hydronephrosis |
| 31 | ♂ | M. W. | 0 | 33 | 8 | 0 | 160/100 | 135/ 90 | 0 | 0 | 0 | L | 0 | Calculi at 23; colic 6 times |
| 32 | ♀ | A. L. | 0 | 23 | 6 | H | 220/150 | 200/130 | 0 | + | 0 | L | 0 | Marked unilateral hydronephrosis |
| 33 | ♂ | C. J. | + | 58 | 2 | 0 | 160/100 | 140/ 90 | ± | 0 | 0 | L | IV++ | Renal damage after alkali at 52 |
| 34 | ♂ | I. L. | 0 | 44 | 10 | Ce | 180/125 | 170/115 | + | 0 | 0 | L | IV+++ | Nephritis after sun lamp burn at 44 |
| 35 | ♀ | M. D. | + | 24 | 0 | H | 200/130 | 175/105 | 0 | 0 | 0 | L | 0 | Marked ptosis with pain |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 34 | ♀ | L. L. | 0 | 44 | 16 | Ce | 180/125 | 170/110 | 0 | 0 | 0 | L | 0 | *Marked ptosis with pain* |
| 35 | ♀ | M. B. | + | 24 | 9 | H | 200/130 | 175/105 | 0 | 0 | 0 | L | 0 | *Marked ptosis with pain* |
| | | | | | | | | | | | | | | **Possible Renal Disease—Albuminuria Before Onset** | |
| 36 | ♂ | F. M. | 0 | 34 | 7 | H-C | 200/150 | 200/130 | 0 | ++++ | R | D-R | IV+ | Albuminuria at 21-25 | |
| 37 | ♂ | R. R. | 0 | 28 | 21 | C | 180/120 | 170/110 | ? | ? | C | D-C | IV+ | Albuminuria at 27 | |
| 38 | ♀ | C. T. | 0 | 31 | 16 | H-C | 210/120 | 180/115 | + | + | C | D-C | 0 | Albuminuria with infection and pain at 28 | |
| 39 | ♀ | E. Z. | 0 | 45 | 12 | H-C | 200/130 | 180/105 | + | 0 | C | L | III+ | Albuminuria at 43 | |
| 40 | ♂ | R. B. | 0 | <45 | >5 | H | 260/140 | 240/115 | + | ++ | 0 | D-? | IV+ | Albuminuria and colic at 44 | |
| 41 | ♂ | H. M. | 0 | <39 | ? | 0 | 160/100 | 150/ 90 | ? | ? | ? | ? | IV+ | Albuminuria at 39, no filling R kidney in pyelogram | |
| 42 | ♂ | W. M. | + | 47 | 7 | H-C | 200/120 | 170/110 | + | + | 0 | D-R | 0 | Albuminuria at 46 | |
| 43 | ♂ | B. R. | + | 50 | 15 | 0 | 230/130 | 190/110 | + | 0 | C-R-Ce | D-R | IV+ | Albuminuria at 48 | |
| | | | | | | | | | | | | | | **Possible Renal Disease—Miscellaneous** | |
| 44 | ♂ | F. E. | + | 40 | 7 | [illegible] | 230/140 | 200/120 | + | ++ | C-Ce | D-Ce | IV++ | Hydroureter at autopsy | |
| 45 | ♂ | J. O. | 0 | 32 | 2 | 0 | 220/140 | 190/130 | 0 | 0 | 0 | L | 0 | Pyuria | |
| 46 | ♂ | C. G. | + | 34 | 7 | C | 190/120 | 155/100 | ± | 0 | C | L | 0 | Pyuria | |
| 47 | ♂ | J. D. | + | 21 | 10 | H | 160/ 90 | 145/ 85 | 0 | 0 | ? | L | 0 | Hematuria before onset | |
| 48 | ♂ | J. K.† | 0 | 29 | 9 | H | 280/170 | 230/130 | 0 | + | R | D-R | II+++ | Albuminuria at onset | |
| 49 | ♂ | F. M.* | 0 | 17 | 9 | C-Ce | 230/135 | 185/130 | 0 | ++ | R | D-R | II++ | Albuminuria at onset | |
| 50 | ♂ | A. R.† | 0 | 30 | 16 | H-C | 280/190 | 220/150 | + | ++ | C-R | D-R | II++ | Calculus at 40 | |
| 51 | ♂ | J. C. | 0 | 36 | 4 | H | 280/150 | 250/140 | + | ++ | R-Ce | D-R | IV+ | Albuminuria and hematuria at onset, marked | |
| 52 | ♂ | M. M. | + | 34 | 5 | H | 170/120 | 145/100 | 0 | 0 | 0 | L | 0 | Pyuria | |
| 53 | ♂ | P. F. | + | 36 | 8 | H | 150/ 85 | 130/ 90 | 0 | 0 | 0 | L | 0 | Pyuria | |
| 54 | ♂ | A. F. | 0 | 33 | 11 | 0 | 210/130 | 180/120 | 0 | 0 | 0 | L | IV+ | Pyuria | |
| 55 | ♂ | H. K. | 0 | 24 | 3 | 0 | 240/160 | 200/140 | 0 | 0 | 0 | L | 0 | No filling R kidney on pyelography | |
| 56 | ♂ | H. E. | 0 | 42 | 14 | 0 | 220/115 | 200/110 | + | 0 | 0 | L | 0 | ? Renal failure with recovery at 49 | |
| **Summary:** | | | 36%+ | Average 33.4 yr. | Average 7.5 L 6.9 D | 54% H <35% C Ce | 221/138 | 190/117 | 43%+ | 65%+ | | 62% D (70% with renal failure) | | | |

* Cases previously reported.[13]

† Cases previously reported.[29b]

‡ + = hypertension in family of one parent; ++ = hypertension in family of both parents.

§ Age at which hypertension was first discovered. Unless so indicated, the blood pressure is known to have been normal within two years previous to this age. The age of onset is known, in many cases, within one year.

‖ To the present (1938) or to death.

¶ Symptoms: H = headaches; C = cardiac insufficiency or pain; Ce = cerebral vascular "spasm," apoplexy, transient paralyses or "hypertensive encephalography"; zero = none.

‡‡ The figures given indicate the approximate highest and lowest levels of both systolic and diastolic pressure, measured over a period of several days for each. Single extreme readings are not given. Measurements within a year following neurosurgery are not given.

** Arteriosclerosis—i. e., tortuosity of vessels, narrowing, increased light reflex, arteriovenous constriction. Hemorrhage, or exudate—i. e., perivasculitis, scars, exudate, fresh and old hemorrhage, papilledema.

†† C = cardiac failure or coronary accident; R = renal failure or insufficiency, moderate or severe; Ce = apoplexy, "spasm," paralysis, or hypertensive encephalopathy.

§§ L = living; D = dead; C = cardiac failure or coronary accident; R = renal insufficiency; A = apoplexy; ? = unknown.

# When one or more of the criteria for classifying the case in another group are present, this is indicated. These criteria are graded from + to ++++, and indicate cases with the significant findings of two groups only when graded +++ or ++++.

Of the patients in this group 44 were males and 12 were females. Thirty-four died, the average duration of their disease being six and nine-tenths years. Twenty-four died of renal failure or of renal and cardiac failure together, 4 primarily of cardiac failure, 3 of cerebral accidents and 1 of anuria following a cystoscopic examination. The manner of death in 2 instances is unknown. Fifteen patients lived four years or less after the onset of hypertension. Reports of 2 cases as examples follow.

CASE 3 (table 2).—J. C.[13] was a 38 year old Italian subway worker. His past history was irrelevant. There was nothing in his family history to account for the presence of hypertension. At the age of 27 he had an infection of the upper respiratory tract, which was followed by edema of the face and ankles, dyspnea and scanty output of urine. He entered the St. Francis Hospital, where a diagnosis of acute nephritis was made. The systolic blood pressure was 190 mm. of mercury and the diastolic was 100. There were edema, albuminuria, hematuria and fever. After he had been at rest in bed a month, edema disappeared and the blood pressure fell to 150 systolic and 85 diastolic. He was discharged, although albuminuria persisted. He was well until the age of 35 when he had a sudden pain in the region of the right kidney, followed by pain on urination. On cystoscopic examination at the Fordham Hospital a renal calculus was not found. His symptoms subsided. The systolic pressure was 240 and the diastolic pressure 138. There were many white and red blood cells in the urine. A few months later (July 1935) he was referred to this hospital because of the development of palpitation and dizziness.

The tonsils were chronically inflamed. At the cardiac apex a systolic murmur was heard. The peripheral arteries were moderately thickened. The ocular fundi were normal except for arteriolar constriction. The heart was not enlarged on roentgen examination. The arterial systolic pressure, measured almost daily for a month, averaged 210, and the diastolic pressure 130. By the standard Van Slyke test urea clearance was 101 per cent of normal, and the kidneys after fluid had been withheld for twenty-four hours were able to concentrate urine to a specific gravity of 1.027. There was no albuminuria and no abnormal increase in the microscopic elements.

On October 14 both splanchnic nerves were resected above the diaphragm. The course of the disease apparently was not influenced. For two years the condition of the patient remained unchanged except for a rise in blood pressure to 260 systolic and 150 diastolic. Hemorrhages and exudate appeared in the ocular fundi.

In May 1938 a second attack of pain referable to the right kidney occurred, which was followed by hematuria and passage of "gravel." The urea clearance[14] then had fallen to 49 per cent, and the maximal concentration of the urine[15] showed a specific gravity of 1.022. Renal function soon became rapidly reduced, many hemorrhages were found in the retina, and five months later retention of

13. This case has previously been reported (Page, I. H., and Heuer, G. J.: The Effect of Splanchnic Nerve Resection on Patients Suffering from Hypertension, Am. J. M. Sc. **193**:820 [June] 1937).

14. By "urea clearance" is meant the value obtained by application of the standard Van Slyke test.

15. By "maximal concentration of the urine" is meant the nonprotein specific gravity of the urine after fluids have been withheld for twenty-four hours.

nitrogen was discovered. The patient died of uremia in November 1938. Autopsy showed chronic glomerulonephritis, generalized arteritis and hypertrophy of the heart.

*Summary.*—An attack of acute nephritis was followed some time later by persistent arterial hypertension with normal renal function. The clinical appearance was typical of "essential" hypertension until six months before death. At autopsy the lesions of chronic glomerulonephritis were observed.

CASE 30 (table 2).—J. G., a 31 year old unemployed man, had had albuminuria for as long as he could remember. He passed an examination for life insurance, however, at the age of 20. One year later the blood pressure was 180 systolic and 110 diastolic. In 1931, at the age of 24, the systolic pressure was 150 and the diastolic pressure 100. The patient complained of few symptoms referable to hypertension until the age of 28, when fatigue and palpitation appeared. The blood pressure was then said to be very high. At 29 the systolic pressure was found (at the Brooklyn Hospital) to be 220 and the diastolic pressure 110. Various tests of renal function were said to have given normal results. He was first seen in this clinic in May 1936.

The physical examination gave essentially negative results. The vessels of the fundi were somewhat tortuous. The heart was shown slightly enlarged in the roentgenograms. The results of numerous urea clearance tests varied markedly, indicating a range of from 75 to 176 per cent of normal. The maximal specific gravity of the urine was 1.023. The excretion of protein in the urine was usually very slight but on one occasion amounted to as much as 1.97 Gm. in twenty-four hours. The systolic pressure, recorded almost daily for a month, ranged between 228 and 190 and the diastolic pressure between 130 and 100, the lower figures having been observed after prolonged rest in bed. The blood pressure rose to a higher level during the next two and one-half years, usually varying between 140 and 150 diastolic. A significant change in renal function did not occur, although the size of the cardiac shadow increased slightly.

On intravenous injection of 20 cc. of diodrast, pyelograms disclosed the presence of bilateral hydronephrosis of moderate degree with constriction at the ureteropelvic junction. Proteinuria was greater when the patient was out of bed. Cystoscopic examination in November 1938 confirmed the diagnosis of bilateral hydronephrosis, most marked on the right, with angulation of the ureter. The patient died of anuria after examination.

*Summary.*—Albuminuria persisted for many years. The onset of hypertension was placed at the age of 21. There existed, at the same time, bilateral hydronephrosis, probably due to a congenital renal abnormality. Except for this important lesion, the clinical appearance was that of "essential" hypertension.

## II. DISORDERS OF THE NERVOUS SYSTEM

In 1935, Page[16] described a symptom complex occurring in young women suffering from essential hypertension which he called the "hypertensive diencephalic syndrome." Characteristic of this disease are attacks of: (1) curious, irregular, blotchy blushing, first of the face, then spreading to the neck, the trunk and sometimes the abdomen; (2) spontaneous crying or watering of the eyes; (3) excessive perspiration,

16. Page, I. H.: A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, Am. J. M. Sc. **190**:9 (July) 1935.

TABLE 3.—*Hypertensive Diencephalic Syndrome* ##

| Case No. | Sex | Patient | Family† History | Age at Onset,‡ Years | Duration,§ Years | Symptoms¶ When First Seen | Average Extremes‡‡ of Blood Pressure, Mm. Hg | | Ocular Fundi** | | Progress†† | Present State§§ | Other Classifying Signs## | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Highest | Lowest | Arteriosclerosis | Hemorrhage or Exudate | | | | |
| **Diencephalic Syndrome—Marked** | | | | | | | | | | | | | | |
| 1 | ♀ | R. H.† | 0 | 16 | 6 | H | 180/130 | 140/ 90 | 0 | 0 | 0 | L | 0 | Marked emotional tension |
| 2 | ♀ | B. H.† | + | 24 | 11 | 0 | 230/140 | 160/110 | 0 | 0 | 0 | L | 0 | Onset with pregnancy |
| 3 | ♀ | M. L.† | 0 | 22 | 14 | 0 | 270/160 | 190/130 | 0 | 0 | 0 | L | 0 | Onset with pregnancy |
| 4 | ♀ | C. D. | 0 | 28 | 13 | H | 220/120 | 190/110 | 0 | 0 | 0 | L | 0 | Onset with pregnancy |
| 5 | ♀ | R. D. | 0 | 28 | 11 | H | 280/160 | 190/120 | 0 | +++ | R | D-R | 0 | Onset with pregnancy |
| 6 | ♀ | M. C.* | ++ | 37 | 13 | H | 230/120 | 190/100 | 0 | 0 | 0 | L | 0 | Onset with pregnancy |
| 7 | ♀ | A. R.† | 0 | 23 | 7 | H | 230/140 | 180/120 | 0 | 0 | ?R | L | 0 | |
| 8 | ♀ | L. R. | + | 39 | 11 | 0 | 270/145 | 200/100 | + | 0 | ?R | L | 0 | Epileptiform convulsions |
| 9 | ♀ | T. L. | 0 | 33 | 8 | H | 210/130 | 165/ 95 | + | + | 0 | L | 0 | |
| 10 | ♀ | M. S.* | 0 | 32 | 5 | H | 220/140 | 200/120 | + | 0 | 0 | L | IV+ | |
| 11 | ♀ | E. B. | 0 | 19 | 10 | H | 220/140 | 160/100 | 0 | 0 | 0 | L | 0 | Epilepsy and rheumatic heart |
| 12 | ♀ | M. O.* | 0 | 22 | 6 | H | 200/130 | 180/120 | 0 | 0 | 0 | L | 0 | |
| 13 | ♀ | H. R. | ++ | 42 | 3 | 0 | 190/115 | 160/ 95 | 0 | 0 | 0 | L | 0 | Cerebral hemangioma |
| 14 | ♀ | S. F. | ++ | <30 | >7 | H | 250/140 | 190/110 | + | 0 | 0 | L | 0 | |
| 15 | ♀ | E. C. | + | 26 | 20 | H | 250/140 | 185/100 | + | 0 | Ce | L | 0 | |
| 16 | ♂ | M. S. | + | 18 | 21 | H | 210/150 | 170/110 | 0 | 0 | 0 | L | 0 | Marked emotional tension |
| 17 | ♂ | L. R. | 0 | 32 | 11 | 0 | 165/ 90 | 140/ 85 | + | 0 | 0 | L | 0 | |
| 18 | ♀ | A. L. | 0 | 22 | 8 | H | 230/130 | 180/120 | + | 0 | 0 | L | 0 | |
| **Diencephalic Syndrome—Moderate** | | | | | | | | | | | | | | |
| 19 | ♀ | G. F. | 0 | 20 | 4 | 0 | 200/130 | 130/100 | 0 | 0 | 0 | L | 0 | Bell's palsy at 22 |
| 20 | ♀ | I. S.† | 0 | 22 | 6 | 0 | 190/120 | 150/ 90 | 0 | 0 | 0 | L | 0 | Marked emotional instability |
| 21 | ♀ | F. S.† | 0 | 32 | 7 | H | 230/140 | 190/110 | 0 | 0 | 0 | L | 0 | |
| 22 | ♀ | S. H. | + | <38 | >13 | H | 220/115 | 185/ 90 | + | 0 | 0 | L | 0 | |
| 23 | ♀ | J. T. | 0 | 17 | 15 | 0 | 270/140 | 185/125 | + | 0 | 0 | L | 0 | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | ♀ | A. R. | 0 | 39 | 9 | 0 | 220/115 | 155/100 | + | 0 | ?Ce | L | IV++ | |
| 25 | ♀ | G. L. | + | 34 | 4 | H | 200/130 | 150/ 90 | 0 | 0 | 0 | L | I+ | Ptosis of kidney |
| 26 | ♀ | M. B. | 0 | <39 | > 3 | 0 | 175/110 | 145/ 95 | +++ | + | 0 | L | 0 | |
| 27 | ♀ | M. M. | 0 | 25 | 5 | H | 235/ 90 | 210/ 70 | ? | ? | 0 | L | 0 | Onset with pregnancy, aortic insufficiency |
| 28 | ♀ | I. Z. | 0 | <38 | > 6 | C | 250/130 | 210/115 | + | 0 | C | L | 0 | Cardiac pain |
| 29 | ♀ | B. L. | + | 42 | 18 | H | 250/110 | 180/ 90 | + | 0 | C | L | IV+ | Late onset |
| 30 | ♀ | S. D. | + | 38 | 11 | 0 | 170/105 | 130/ 90 | 0 | 0 | 0 | L | 0 | Onset with pregnancy |
| 31 | ♂ | S. F. | 0 | 26 | 7 | H | 185/100 | 145/ 85 | 0 | 0 | 0 | L | 0 | Marked emotional tension |
| 32 | ♂ | H. S. | 0 | 28 | 2 | H | 220/130 | 165/110 | 0 | 0 | 0 | L | 0 | Epilepsy |
| 33 | ♂ | G. V.† | 0 | 18 | 6 | 0 | 230/150 | 170/120 | 0 | 0 | 0 | L | 0 | Postoperative paraplegia |
| 34 | ♂ | E. S.† | + | 33 | 8 | H | 250/150 | 170/100 | 0 | 0 | C | D-C | IV+ | Died coronary occlusion (postoperative) |
| 35 | ♀ | D. S.† | 0 | 34 | 5 | 0 | 290/160 | 210/120 | + | ++ | 0 | D | 0 | Died of meningitis (postoperative) |
| 36 | ♀ | M. W. | + | 19 | 3 | 0 | 260/150 | 215/125 | 0 | +++ | R | D-R | 0 | Malignant course |
| 37 | ♀ | S. J. | 0 | <38 | > 2 | C | 290/170 | 240/140 | + | ++++ | C-R | D-C-R | IV+ | Malignant course |
| | | | | | | | Miscellaneous with Diencephalic Syndrome | | | | | | | |
| 38 | ♀ | A. B. | + | 25 | 4 | H | 220/140 | 150/100 | 0 | 0 | 0 | L | I+++ | Renal colic with hematuria at 20 |
| 39 | ♀ | H. B. | + | 36 | 16 | H | 195/115 | 170/100 | + | 0 | 0 | L | I++ IV+ | Marked ptosis of right kidney |
| 40 | ♀ | G. F. | + | 19 | 4 | H | 190/100 | 150/ 80 | 0 | 0 | 0 | L | 0 | Congenital abnormality of spine with paroxysmal hypertension |
| 41 | ♀ | J. O. | 0 | 39 | 12 | H-C | 200/160 | 240/120 | + | 0 | 0 | L | IV++ | Onset with pregnancy; marked calcification of skull |
| 42 | ♀ | T. F. | + | 36 | ? | H | 220/130 | 170/105 | 0 | 0 | ? | L | 0 | Not well followed |
| 43 | ♀ | E. R. | ++ | 22 | 5 | H | 200/120 | 180/100 | 0 | 0 | 0 | L | 0 | Not well followed |
| 44 | ♀ | F. B. | + | 25 | 10 | 0 | 270/160 | 230/140 | + | + | 0 | ? | 0 | Not well followed |
| 45 | ♀ | J. A. | ++ | 19 | ? | H | 220/140 | 170/120 | + | 0 | ? | ? | III+ | Not well followed |
| 46 | ♂ | B. N. | 0 | 33 | 10 | H | 200/140 | 180/110 | ± | 0 | 0 | L | IV++ | Not well followed |
| Summary: | | | 41%+ | Average 28.1 yr. | Average 9.0 L 5.8 D | 62% H 6% C | Average 227/134 | Average 177/107 | 42%+ | 16%+ | | 11% D | | |

## For explanation of symbols and abbreviations, see footnotes to table 2.

often at the site of the blush; (4) palpitation of the heart and increase in the cardiac rate; (5) rise in blood pressure, and (6) coldness of the extremities. Attacks are usually brought on by emotional stimuli but may arise spontaneously. Page pointed out the clinical similarity of this syndrome to "diencephalic autonomic epilepsy," described by Penfield.[17] Crisler and Allen[18] have recently reported 4 similar cases, in 1 of which the blood pressure was approximately normal.

We have included in this group patients without evidence of renal lesions of endocrine disturbance who have the following signs and symptoms: (1) vasomotor instability, as evidenced by a tendency to blush, flushing, rapid changes in the level of the blood pressure, dermographia, coldness of the extremities and attacks of palpitation; (2) emotional instability, as evidenced by spells of spontaneous crying, excessive nervousness and labile temperament; (3) automatic instability, as evidenced by excessive perspiration, salivation and lacrimation, and (4) arterial hypertension. These symptoms, or some of them, are found usually in young women but occasionally in males and in older women. In addition, a history of sexual difficulties is often obtained, either of frigidity or of excessive desire.

Twenty-seven patients[19] exhibited all these signs and symptoms. Nineteen others were subject to most of them and should probably be included in the same class. In this group of 46 only 5 are dead at the time of writing, 2 having died after operation. The average duration of the disease in those still living is nine years, 18 having lived more than ten years. Evidence suggestive of failure of the heart or kidneys has occurred in only 2. Significant changes in the eyegrounds are rare (table 3).

For the current purpose the use of this designation seems suitable, the symptoms being sufficiently distinctive. Eventually it may become desirable to distribute some of these cases among the other groups.

Case 15 (table 3).—E. C., a 44 year old woman, a chef, had been known to have hypertension for twenty years. Her mother, two maternal uncles and a cousin died of this complaint, and two sisters were said to exhibit it. As a child, she had scarlet fever and diphtheria. She had always been moody, overexcitable, impulsive and of a worrying nature. She had been married and divorced twice. At the age of 25 a salpingo-oophorectomy was performed on the left side because of disease in the organs of the pelvis. (This condition had not influenced the menses.) Shortly afterward she began to complain of nervousness and irritability. She began to notice spells of spontaneous crying, palpitation, blushing, cold hands and feet and excessive perspiration. The blood pressure was 160 systolic. She

17. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

18. Crisler, G. R., and Allen, E. V.: The Flushing Syndrome Simulating "Diencephalic Stimulation" and Its Relation to Essential Hypertension, Proc. Staff Meet., Mayo Clin. **12**:219 (April 7) 1937.

19. Five of these cases are dealt with in Page's original report.[16]

subsequently worked in various hospitals as a cook, and fairly good records were available of her blood pressure. At the age of 29 it was 160 systolic and 100 diastolic, at 30 it varied from 215 to 160 systolic and 105 to 90 diastolic, and from then to the age of 35 it fluctuated between 230 and 180 systolic and 150 and 100 diastolic. Marked lability when the pressure was at a higher level was still present three years later, and a four year record showed fluctuations between 270 and 180 systolic and 150 and 115 diastolic. Since the age of 34 she had noticed an increase in blushing, perspiration, coldness of the extremities and spells of spontaneous crying. At 41 she suffered an attack of "hypertensive encephalopathy" and one year later a similar attack. Headaches became more prominent and at times were incapacitating, although for the most part she was able to continue her work. At 43, examination disclosed: extreme lability of the blood pressure, the values varying between 260 and 185 systolic and 135 and 100 diastolic; moderate sclerosis of the vessels of the retina; slight enlargement of the heart in roentgenograms, and a curious blotchy blush appearing on the neck and face as a result of emotional disturbance or during examination. The hands and feet were cold, mottled and often cyanotic, and perspiration was excessive. The maximal specific gravity of the urine was 1.024, and the urea clearance on two occasions was 93 and 78 per cent of normal respectively. The basal metabolism on several tests was within normal limits. The urine was normal.

She had one further attack characterized by cerebral symptoms, for which she entered the hospital. The blood pressure remained labile.

*Summary.*—At the time of writing, this patient has been suffering from arterial hypertension and the "hypertensive diencephalic syndrome" for twenty years. Cerebral symptoms are beginning to appear. There is little evidence of damage to the heart or the kidneys. The extreme lability of the blood pressure is noteworthy.

### III. ENDOCRINE DYSFUNCTION

That endocrine disturbance plays a role in hypertension has seemed possible to investigators for many years. Malfunction of the pituitary gland, in particular, has been seriously considered as an important factor. Basophilic infiltration of the posterior lobe has been described a number of times,[20] but its importance remains undetermined. A number of syndromes of endocrine dysfunction with hypertension have been reported. Reisman [21] in 1919 described "non-goitrous thyrotoxic hypertension," and Mannaberg [22] also noticed such a condition. Boas and Shapiro [23] reported 27 cases of this condition, pointing out certain notable clinical characteristics: that the basal metabolic rate was often

20. Leary, O. C., and Zimmerman, H. M.: Basophil Infiltration in the Neurohypophysis, Am. J. Path. **13**:213 (March) 1937.

21. Reisman, D.: Hypertension in Women, J. A. M. A. **73**:330 (Aug. 2) 1919.

22. Mannaberg, J.: Arterieller Hochdruck und gesteigerter Grundumsatz, Wien. klin. Wchnschr. **37**:84 (Jan. 24) 1924.

23. Boas, E. P., and Shapiro, S.: (*a*) Diastolic Hypertension with Increased Basal Metabolic Rate, J. A. M. A. **84**:1558 (May 23) 1925; (*b*) Further Observations on Patients with Hypertension and Increased Basal Metabolic Rate, Am. Heart J. **1**:643 (July) 1926.

TABLE 4.—*Endocrine Dysfunction* ##

| Case No. | Sex | Patient | Family† History | Age at Onset,§ Years | Duration,‖ Years | Symptoms¶ When First Seen | Average Extremes‡‡ of Blood Pressure, Mm. Hg | | Ocular Fundi** | | Progress†† | Present State§§ | Other Classifying Signs## | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Highest | Lowest | Arteriosclerosis | Hemorrhage or Exudate | | | | |
| | | | | | | "Nongoitrous Thyrotoxic Hypertension" | | | | | | | | |
| 1 | ♀ | M. W. | + | 31 | 8 | H | 270/160 | 250/140 | + | ++ | C-Ce | D-Ce | II++++ | B. M. R.¶¶ + 29; onset with pregnancy |
| 2 | ♀ | M. G. | 0 | 21 | 9 | H | 240/150 | 150/100 | 0 | ++++ | 0 | L | II++++ | B.M.R. + 27; onset with pregnancy |
| 3 | ♀ | T. G.* | 0 | 34 | 7 | H | 210/120 | 170/110 | ± | 0 | 0 | L | II+++ | B.M.R. + 25; onset with pregnancy |
| 4 | ♀ | M. S. | 0 | 30 | 8 | H | 230/140 | 210/110 | + | 0 | 0 | L | II++++ | B.M.R. + 33; onset with pregnancy |
| 5 | ♀ | D. B. | + | 20 | 1 | C | 250/190 | 230/150 | 0 | +++ | C-Ce | D-C-Ce | II++ | B.M.R. + 35 |
| 6 | ♀ | J. B. | 0 | 20 | 3 | H | 270/160 | 200/120 | ++ | ++ | C-R | D-C-R | II+++ | B.M.R. + 35 |
| 7 | ♀ | M. K. | + | <32 | > 1 | H | 240/170 | 200/140 | + | ++ | C | D-C | II++++ | B.M.R. + 37 |
| 8 | ♀ | L. H. | 0 | 30 | 1 | H-C | 260/170 | 200/140 | ++ | ++ | C-R | D-C-R | 0 | B.M.R. + 34 |
| 9 | ♀ | B. H. | + | <30 | > 1 | H-C | 240/140 | 220/130 | 0 | + | C-R | D-C-R | 0 | B.M.R. + 24 |
| 10 | ♀ | J. P. | + | 42 | 7 | Ce | 230/140 | 190/115 | + | 0 | Ce | L | IV+ | B.M.R. elevated; onset with menopause |
| 11 | ♀ | G. A. | + | 40 | 6 | H-C | 240/150 | 210/110 | ++ | + | C-R | D-C-R | IV++ | B.M.R. + 20; obesity worst with pregnancy; pituitary basophilia |
| 12 | ♀ | S. T. | 0 | 23 | 13 | H | 240/125 | 180/120 | 0 | + | 0 | L | 0 | B.M.R + 20; obesity; onset with pregnancy |
| 13 | ♀ | M. P. | 0 | <40 | > 2 | H | 260/145 | 200/100 | ++ | 0 | C | D-C | II+++ | B.M.R. + 55 |
| | | | | | | Hyperthyroidism Before Onset | | | | | | | | |
| 14 | ♀ | R. S. | + | <48 | > 4 | 0 | 250/130 | 210/110 | 0 | 0 | 0 | L | II+++ | B.M.R. + 24. Operation for nodular goiter; obese |
| 15 | ♀ | K. E. | 0 | 42 | 9 | H | 220/140 | 170/110 | + | 0 | 0 | L | II++IV+ | Exophthalmic goiter at 39; B.M.R. + 52; now normal |
| 16 | ♀ | D. D. | 0 | 19 | 16 | Ce | 260/150 | 190/125 | 0 | 0 | Ce | L | II++ | Thyroidectomy for exophthalmic goiter at 24; B.M.R. now normal |
| 17 | ♀ | J. Z. | 0 | 38 | 5 | H-C | 220/130 | 210/120 | 0 | ± | C | L | 0 | Thyroidectomy for exophthalmic goiter at 32; B.M.R. now normal; obesity |
| 18 | ♀ | E. A. | + | 30 | 10 | H-C | 240/140 | 200/130 | + | 0 | ? | D-? | 0 | Exophthalmic goiter treated; followed by obesity |
| 19 | ♀ | D. B. | 0 | 26 | 20 | H | 250/140 | 160/100 | ± | ± | C-R-Ce | D-R | IV+++ | Exophthalmic goiter at onset with recovery |
| 20 | ♂ | J. P. | 0 | 37 | 7 | H | 230/140 | 170/100 | 0 | 0 | 0 | L | II++ | Toxic nodular goiter; thyroidectomy, 38 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Onset with Menopause** | | | | | | | | | | | | | |
| 21 | ♀ | M. F. | 0 | 44 | 16 | H | 250/150 | 185/ 90 | + | 0 | 0 | L | IV+ Obesity |
| 22 | ♀ | C. C. | 0 | <50 | >14 | C | 180/110 | 145/ 90 | + | 0 | C | L | IV++ Obesity |
| 23 | ♀ | H. S. | 0 | 42 | 4 | H | 240/120 | 200/110 | ? | ? | R | D-R | IV+ Obesity |
| 24 | ♀ | A. K. | 0 | 50 | 14 | 0 | 190/110 | 140/ 90 | 0 | 0 | 0 | D | 0 Obesity; died of cancer |
| 25 | ♀ | A. S. | 0 | 42 | 9 | H | 190/110 | 160/100 | ++ | 0 | 0 | L | IV+ Obesity |
| 26 | ♀ | A. S. | + | 47 | 14 | H-C | 190/110 | 150/ 90 | +++ | 0 | C | L | IV++ Obesity |
| 27 | ♀ | G. H. | + | 47 | 10 | H | 280/180 | 240/120 | + | 0 | ? | D-? | 0 Obesity; albuminuria with pregnancy, 29 |
| 28 | ♀ | M. L. | 0 | 45 | 5 | C | 200/ 90 | 150/ 80 | + | 0 | C-Ce | ? | II++ |
| **Miscellaneous** | | | | | | | | | | | | | |
| 29 | ♀ | R. L. | 0 | 19 | 6 | H | 230/140 | 145/100 | 0 | + | 0 | L | II++++ Marked hirsutism; paroxysmal hypertension at onset |
| 30 | ♀ | G. P. | 0 | 23 | 2 | H | 210/120 | 160/100 | 0 | 0 | 0 | L | II++++ Hirsutism; paroxysmal hypertension at onset; B.M.R. + 35 after subtotal thyroidectomy |
| 31 | ♀ | P. S.† | 0 | 24 | 6 | H | 220/130 | 160/100 | ± | 0 | 0 | L | II++ Hirsutism at onset with pregnancy; irregular menses |
| 32 | ♀ | A. S.† | + | 23 | 6 | H | 220/140 | 190/130 | 0 | 0 | 0 | L | II++++ Hirsutism and menorrhagia at onset |
| 33 | ♀ | A. C.° | 0 | 16 | 3 | H-Ce | 260/180 | 220/150 | + | ++++ | C-R-Ce | D-C-R | 0 Neuroblastoma of the adrenal |
| 34 | ♀ | F. R. | 0 | <43 | > 6 | H-C | 220/130 | 170/110 | 0 | 0 | C | L | IV+ Cushing's syndrome |
| 35 | ♀ | F. D. | 0 | 42 | 9 | H-C | 280/150 | 240/130 | + | + | R-Ce | D-Ce | IV+++ Probable Cushing's syndrome |
| 36 | ♀ | L. L. | 0 | 43 | 2 | H-C | 200/120 | 150/ 90 | +++ | + | ? | D-? | II++ Probable Cushing's syndrome |
| 37 | ♀ | M. M. | ++ | 30 | 32 | H | 230/120 | 160/ 90 | + | 0 | 0 | L | IV++ Myxedema and obesity |
| 38 | ♂ | A. R. | 0 | 64 | 4 | H | 200/150 | 180/110 | + | 0 | C | L | IV++ Hypothyroidism |
| 39 | ♀ | A. Z. | 0 | 43 | 11 | H | 260/140 | 190/120 | + | 0 | 0 | L | II++IV+ Onset with menopause; obesity; marked calcification of skull |
| 40 | ♀ | E. K. | 0 | <29 | >10 | H-C | 200/125 | 180/110 | 0 | 0 | ? | D-? | IV++ Obesity of trunk |
| 41 | ♀ | L. G. | 0 | 30 | 7 | C | 270/160 | 240/130 | + | ± | C-Ce | D-? | II++IV+ Obesity of trunk |
| 42 | ♀ | J. R. | 0 | 27 | 11 | H | 230/140 | 180/110 | ± | 0 | 0 | L | II++ Sudden obesity at 27 |
| 43 | ♀ | M. S. | 0 | <42 | > 3 | C | 210/120 | 190/110 | 0 | 0 | C | L | 0 Tremendous obesity; toxemia of pregnancy twice |
| Summary: | | | 28%+ | Average 34.8 yr. | Average 9.4 L 6.2 D | 79% H >42% C Ce | Average 233/139 | Average 182/114 | 55%+ | 31%+ | | 43% D (54% with renal failure) | |

†‡ For explanation of symbols and abbreviations, see footnotes to table 2.
¶¶ Basal metabolic rates are the lowest recorded.

markedly elevated without many of the signs of exophthalmic goiter and that thyroidectomy or administration of iodine had no effect on it. "Menopausal hypertension" has sometimes been considered a separate syndrome.[24] Fishberg[3] has observed hypertension following exophthalmic goiter and has also observed that it is associated with myxedema. It has often been noticed in cases of marked obesity. Herrick[25] reported the occurrence of the triad hypertension, obesity and diabetes.

The subjects of our own study were therefore examined for evidence of endocrine disturbance. This was found in 41 women and 2 men. In 13 patients it corresponded to the type described by Boas and Shapiro, the basal metabolic rates being elevated without obvious exophthalmic or nodular goiter. Seven patients gave histories of thyrotoxicosis antedating or appearing near the time of onset of hypertension. In 9 patients hypertension began at the menopause; 8 of these were obese. The onset in 4 was associated with rapid development of hypertrichosis. Three had many of the signs of Cushing's syndrome. Four were markedly obese. In others hypertension was associated with a variety of endocrine disturbances (table 4).

The diencephalic syndrome was prominent in 7 of the 13 patients with "non-goitrous thyrotoxic hypertension" and in 4 other patients with definite endocrine disturbance. Of the 43 patients in this group, 18 are dead at the time of this report. The cause of death was: in 3, cardiac; in 5, cardiac and renal; in 2, renal; in 2, cerebral, and in 6, either unrelated to hypertension or unknown. Of the living patients still being studied (24) 8 have shown severe cerebral manifestations or signs or symptoms of failure of the heart or of the kidneys. Almost all (96 per cent) have symptoms, which are often severe, headache being especially prominent.

Case 5 (table 4).—D. B., a 22 year old stenographer, had scarlet fever at the age of 7 years and diphtheria a year later. Her father died at the age of 54 of heart disease, when she was 20. She was perfectly well until his death, which was a great shock to her and from which she dated her symptoms. She began to tire easily and became excessively nervous. She lost no weight.

The basal metabolic rate was +34 and +37 per cent. The pulse rate was elevated. The rate of phenolsulfonphthalein excretion was 60 per cent in two hours. The systolic pressure was 190 and the diastolic pressure 150. Iodine medication was prescribed, but the basal metabolic rate remained high (+48 per cent) and the pulse rate rapid (125). Severe occipital headaches began, which were often incapacitating. One year later she noticed dyspnea on exertion, occasional attacks orthopnea and swelling of the ankles. The systolic pressure rose to 210 and the diastolic pressure to 150. Dyspnea became rapidly worse. She was admitted to this hospital, Dec. 16, 1933.

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24. Huchard, H.: Traité clinique des maladies du cœur et de l'aorte, ed. 3, Paris, O. Doin, 1899, vol. 1, p. 74.

25. Herrick, W. W.: Hypertension and Hyperglycemia, J. A. M. A. **81**:1942 (Dec. 8) 1923.

The patient was slightly orthopneic. The ocular fundi showed slight papilledema. The arteries were constricted almost to obliteration, with marked perivasculitis; there were a few small hemorrhages and large patches of white exudate. The thyroid gland was not enlarged, and there was no tremor of the hands. Von Graefe's sign was not present. There was congestion at the bases of both lungs. The heart was enlarged and markedly overactive, and there was gallop rhythm. The systolic pressure was 220 and the diastolic 180. There was no edema. The urea clearance was 43 per cent of normal. The maximal specific gravity of the urine was 1.015. There were moderate albuminuria and microscopic hematuria. The systolic pressure during two weeks varied from 228 to 250 and the diastolic from 188 to 150. The pulse rate remained between 100 and 140. A sudden cerebral accident terminated the illness. At autopsy there were cerebral hemorrhage, early arteriolar sclerotic nephritis, arteriolar sclerosis, hypertrophy of the heart and diffuse basophilism of the pituitary gland.

*Summary.*—This patient had a "malignant" form of arterial hypertension, death from a cerebral accident taking place two years after the onset. Although the basal metabolic rate was elevated, the usual signs of hyperthyroidism were lacking. The diastolic pressure was exceptionally high. The pituitary gland on microscopic examination showed an abnormality.

CASE 21 (table 4).—M. F., a 60 year old housewife, had scarlet fever and diphtheria at an early age. Her mother died of apoplexy at 80. There was no definite family history of hypertension. Of her 4 children, 2 were premature. She was in excellent health until the age of 44, when symptoms of menopause appeared. Coincidentally she noticed severe occipital headaches, and high blood pressure was discovered. As the menopause became established the headaches became worse, but they were never incapacitating.

At 49 she was moderately obese. The heart was normal on roentgen examination; the peripheral vessels were normal; the systolic pressure was 245 and the diastolic 150. The urine was normal. The vessels of the ocular fundi were slightly tortuous. The urea index of Van Slyke was normal. The patient excreted 74 per cent of phenolsulfonphthalein in two hours. The maximal specific gravity of the urine was 1.030. The systolic pressure varied during six weeks' observation from 270 to 200 and the diastolic pressure from 170 to 130. During the next seven years the headaches continued with lessened severity. Other changes were noticed: There was a gradual decline in the blood pressure (which at the time of writing is usually between 220 and 180 systolic and 120 and 110 diastolic); a fall in the clearance of urea from 93 per cent of normal at the age of 53 to 65 per cent at the age of 56, with a decrease in the maximal specific gravity of the urine to 1.025, some increase in the tortuosity of the vessels of the ocular fundi and a slight increase in the size of the heart. During the past three years she has been free from symptoms.

*Summary.*—Arterial hypertension, beginning with the menopause, is now of sixteen years' duration. There has been a progressive decrease both in the blood pressure and in the symptoms.

## IV. VASCULAR DISEASE

Generalized arteriosclerosis and "essential" hypertension are often found in association. The frequency with which these two conditions occur together suggests that there is some intimate relation between

them, but the nature of this relation is not clear. Although Lange[26] concluded that arteriosclerosis may result from hypertension, he admitted that the arterial changes typical of hypertension are confined to hypertrophy of the media. It is known, however, that arteriosclerosis does not always accompany the long-standing hypertension associated with coarctation of the aorta, and it seems uncertain that hypertension alone produces true arteriosclerosis.

Severe generalized arteriosclerosis often occurs without elevation of the diastolic pressure—that is, without arterial hypertension—although the systolic pressure may be elevated, probably owing to a loss of arterial elasticity. The only situation in which hypertension has been believed to result from arteriosclerosis is one in which the renal arteries or their mouths are narrowed by sclerotic changes.[27]

The commonest form of "essential" hypertension, that observed in older persons, is so often associated with generalized arteriosclerosis that it seems desirable to form a separate group of cases on this basis alone. The usual benign course, ending in heart failure or, more commonly, in a cerebral accident, the absence of symptoms (such as palpitation or headache) and the lack of retinal exudation supply reasons on clinical grounds for regarding such cases as a separate group. In 36 patients (28 men and 8 women) generalized arteriosclerosis was found without other phenomena significant enough to permit placing their cases in one of the other groups.

Twenty of these patients died—9 of a cerebral accident, 2 of cardiac failure, 3 of renal failure and 3 of other diseases. The manner in which the remaining 3 died is unknown. In 2 of those who died in uremia the renal arteries at autopsy were markedly narrowed by sclerotic changes.

The onset of hypertension in 6 (of 36 patients) occurred after the age of 60, in 11 between 50 and 60, in 10 between 40 and 50 and in 7 between 35 and 40. At the time of this report severe symptoms are present in 5 (of 15) living patients. Three have been stricken with cerebral accidents. Severe headaches and palpitation are unusual.

One case of hypertension associated with Buerger's disease and 1 of hypertension associated with lead poisoning are included in this group.

Case 5 (table 5).—J. K. was a retired barber 72 years old. His mother had died at 78 of "hardening of the arteries." Two brothers died of tuberculosis. The patient suffered an attack of diphtheria at the age of 10 years. At 30 he contracted a chancre, which was treated with mercury bichloride given by mouth. The Wassermann reaction was negative on many occasions. At 38 the patient was found to have pulmonary tuberculosis and was treated for two years in a sanatorium. Roentgen examinations disclosed some pulmonary fibrosis but no evidence

26. Lange, F., in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933, chap. 18.

27. Goldblatt, H.: Personal communication to the authors.

Table 5.—*Vascular Disease #1*

TABLE 5.—*Vascular Disease* ##

| Case No. | Sex | Patient | Family† History | Age at Onset,§ Years | Duration,‖ Years | Symptoms¶ When First Seen | Average Extremes‡‡ of Blood Pressure, Mm. Hg | | Ocular Fundi** | | Progress†† | Present State§§ | Other Classifying Signs## | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Highest | Lowest | Arterio-sclerosis | Hemorrhage or Exudate | | | | |
| **Marked Generalized Arteriosclerosis** | | | | | | | | | | | | | | |
| 1 | ♂ | D. M. | 0 | <70 | > 3 | 0 | 230/120 | 180/100 | + | 0 | 0 | D | 0 | Died of pneumonia |
| 2 | ♂ | J. K. | 0 | <62 | >12 | 0 | 270/ ? | 180/ 90 | ++ | 0 | 0 | D | 0 | Died of pneumonia |
| 3 | ♂ | J. L. | 0 | <61 | > 3 | 0 | 205/115 | 180/ 95 | ? | ? | R | D-R | 0 | Calcification of vessels ¶¶ |
| 4 | ♂ | O. E. | + | 61 | 2 | 0 | 175/100 | 155/ 85 | ++ | 0 | 0 | L | 0 | Calcification of vessels ¶¶ |
| 5 | ♂ | J. K. | 0 | 52 | 20 | C | 230/130 | 210/120 | ++ | 0 | 0 | L | 0 | Calcification of vessels ¶¶ |
| 6 | ♂ | J. S. | + | 50 | 9 | C | 230/130 | 200/110 | ++++ | + | Ce | D-Ce | 0 | Calcification of vessels ¶¶ |
| 7 | ♂ | A. P. | 0 | 47 | 2 | H | 230/140 | 200/120 | +++ | + | Ce | D-Ce | 0 | |
| 8 | ♂ | M. H. | 0 | <39 | > 2 | 0 | 230/150 | 220/130 | ++ | 0 | 0 | D | 0 | Calcification of vessels;¶¶ died of gastric hemorrhage |
| 9 | ♂ | C. L. | 0 | 36 | 8 | H-C | 270/150 | 240/140 | ++++ | + | C-R | D-C-R | 0 | Moderate arteriosclerotic obstruction of renal arteries |
| 10 | ♂ | C. S. | ? | <31 | > 1 | H | 250/150 | 240/140 | ? | ? | R-Ce | D-R | 0 | Marked arteriosclerotic obstruction of renal arteries |
| 11 | ♀ | L. H. | 0 | 62 | 3 | H | 180/110 | 170/ 90 | ++ | 0 | 0 | L | 0 | Pernicious anemia |
| 12 | ♀ | A. W. | + | <58 | >10 | C | 210/105 | 170/ 95 | +++ | 0 | C | D-C | 0 | |
| 13 | ♀ | G. W. | ++ | 51 | 5 | H-C | 190/140 | 160/110 | ++ | + | C-Ce | D-C | 0 | |
| 14 | ♀ | H. K. | + | 50 | 4 | Ce | 260/160 | 230/130 | ++ | ++ | Ce | D-Ce | 0 | |
| **Moderate Generalized Arteriosclerosis** | | | | | | | | | | | | | | |
| 15 | ♂ | W. L. | 0 | 53 | 13 | H | 240/130 | 180/110 | ++ | 0 | Ce | L | 0 | |
| 16 | ♂ | W. W. | + | <56 | >10 | Ce | 190/110 | ..... | ++ | + | ? | D-? | 0 | Calcification of vessels;¶¶ diabetes |
| 17 | ♂ | F. L. | 0 | 53 | 3 | H-Ce | 230/130 | 215/125 | ++ | 0 | ? | D-? | 0 | |
| 18 | ♂ | B. B. | ++ | 52 | 7 | H-C | 200/115 | 140/ 90 | ++ | 0 | C | L | 0 | Obesity |
| 19 | ♂ | G. L. | 0 | 50 | 5 | 0 | 200/120 | 155/ 95 | ++ | 0 | 0 | L | 0 | Auricular fibrillation |
| 20 | ♂ | H. W. | 0 | <47 | > 8 | C-Ce | 230/130 | 190/125 | ++ | 0 | Ce | L | 0 | |
| 21 | ♂ | S. R. | + | <47 | > 5 | C | 200/115 | 150/ 95 | ++ | 0 | C-Ce | D-Ce | 0 | |
| 22 | ♂ | G. C. | 0 | 45 | 6 | 0 | 180/115 | 150/100 | ++ | 0 | 0 | L | 0 | |
| 23 | ♂ | C. S. | 0 | 47 | 7 | Ce | 210/130 | 180/110 | ++ | 0 | Ce | L | 0 | |
| 24 | ♂ | R. L. | 0 | 43 | 4 | 0 | 190/120 | 185/110 | + | 0 | 0 | L | 0 | |
| 25 | ♂ | J. B. | ++ | 43 | 10 | H | 240/140 | 200/120 | ++ | 0 | 0 | L | 0 | |
| 26 | ♂ | W. G. | 0 | 40 | 22 | H | 230/130 | 200/120 | + | 0 | 0 | D-Ce | 0 | |
| 27 | ♂ | J. R. | + | 38 | 7 | 0 | 170/110 | 150/ 90 | + | 0 | 0 | L | 0 | |
| 28 | ♂ | J. G. | + | 36 | 4 | H | 230/130 | 215/110 | 0 | 0 | ? | ? | 0 | Not well followed |
| 29 | ♂ | H. M.† | 0 | <38 | > 3 | C | 260/160 | 180/120 | ++ | 0 | C-Ce | D-Ce | 0 | Obesity |
| 30 | ♂ | J. L. | 0 | 36 | 6 | 0 | 220/150 | 180/110 | + | 0 | C-R | D-Ce | 0 | |
| 31 | ♀ | A. K. | 0 | 53 | 4 | C | 240/130 | 210/105 | + | 0 | Ce | D-Ce | 0 | |
| 32 | ♀ | C. T. | 0 | <66 | ? | H | 170/ 95 | 150/ 85 | ++ | 0 | ? | D-? | 0 | Not well followed |
| 33 | ♀ | H. M. | 0 | 45 | 14 | 0 | 240/120 | 190/110 | + | 0 | C | L | 0 | |
| 34 | ♀ | E. B. | ? | <44 | >23 | 0 | 185/120 | 155/100 | + | 0 | 0 | L | 0 | |
| 35 | ♂ | J. S. | ++ | 36 | 8 | C | 215/145 | 180/120 | + | 0 | Ce | D-Ce | 0 | Thromboangiitis obliterans |
| 36 | ♂ | J. S. | 0 | 22 | 4 | H | 235/140 | 225/135 | + | +++ | R | L | 0 | Lead poisoning |
| | | | 35%+ | Average 48.9 yr. | Average 8.9 L >6.3 D | 36% H >39% C Ce | 219/128 | 183/ 97 | 97%+ | 21%+ | | 57% D (18% with renal failure) | | |

## For explanation of symbols and abbreviations, see footnotes to table 2.
¶¶ In roentgenograms of the extremities.

of active tuberculosis. He was well until the age of 52, when hypertension was discovered. The systolic blood pressure was said to be 170 to 180, and albumin and casts were found in the urine. The blood pressure remained fairly constant until the age of 58, when it began to increase. At the age of 65 the systolic pressure taken on admission to this hospital had reached 230 and the diastolic pressure 130. The only symptoms were slight headache, coming on with excitement, and a moderate amount of dyspnea on exertion, which had been slowly progressing since the age of 61. The patient had three rather profuse epistaxes at 62.

The important physical findings in 1932, at the age of 65 years, were: moderate obesity, marked generalized arteriosclerosis with tortuosity and beading of the larger arteries, moderate pulmonary emphysema and slight enlargement of the prostate. Roentgen examination showed the heart enlarged and the ascending aorta moderately dilated. Calcification in the vessels of the extremities was seen in the roentgenograms. In the six years preceding this report the urea clearance has progressively decreased from 73 to 43 per cent of normal and the maximal concentration of the urine to a specific gravity of 1.021. The retinal arteries are moderately tortuous and thickened; there is constriction of the veins at arteriovenous crossings. The systolic pressure has varied from 230 to 200 and the diastolic pressure from 160 to 120. In November 1937 the patient suffered hemiplegia on the right side, from which he slowly recovered. At present he complains of dyspnea on climbing three flights of stairs, occasional dizzy spells, nocturia and an occasional nosebleed.

*Summary.*—In this patient arterial hypertension has persisted for twenty years, associated with marked general arteriosclerosis with evidence of only minimal damage to the heart, vessels and kidneys. He complains of few symptoms. The progress of the ailment has been slow.

Case 26 (table 5).—W. G., 68 years old, an artist, was known to have had hypertension at the age of 40. His parents died of unknown causes. As a young adult, he contracted gonorrhea, malaria and acute appendicitis. At the age of 54 he had an attack of pneumonia, and two years later he had jaundice with biliary colic, which was relieved without operation. At the age of 40 the systolic pressure was said to be 180. There was some cardiac irregularity, which soon disappeared. Hypertension continued, but he had no symptoms from it until the age of 56, when he noticed that he was obliged to limit his activities. Not until the age of 62 did he complain of mild occipital headaches, slight dizziness and a sensation of transient numbness in the left arm.

At this time (in 1932) he was moderately obese. The systolic pressure varied during three weeks' rest in bed between 230 and 180 and the diastolic between 116 and 100. In the ocular fundi there was moderate beginning arteriosclerosis. The heart was moderately enlarged on roentgen examination. There was some tortuosity of the aorta. A soft systolic murmur was heard at the base of the heart. The peripheral arteries were moderately thickened and slightly tortuous. The urea clearance was 75 per cent of normal. One year later the patient began to complain of nervousness and of some increase in the number of headaches. He was able to continue his work, however, and to live an approximately normal life. Hypertension persisted. At 68 the systolic blood pressure had risen to 230 and the diastolic pressure to 130. This was accompanied by an increase in the size of the heart. The urea clearance was 85 per cent of normal, and there was slight proteinuria. The patient was well except for headaches until the day he died, suddenly, of apoplexy at the age of 68.

*Summary.*—This was a case of long-standing arterial hypertension associated with arteriosclerosis. There were few symptoms. A cerebral accident was the terminal event.

### V. UNCLASSIFIED

There were 37 cases which could not be readily classified according to the scheme adopted in this study. In 10 the facts known were insufficient for a proper diagnosis. Of the remaining 27, although considerable information was available, data which we have come to regard as essential for purposes of this classification were lacking in all but 6. The onset of hypertension occurred in 4 (of these 27 cases) during pregnancy. In 6 hypertension was very mild. Three belonged possibly in group II and 3 in group III. In 5 rapid progress of the "malignant" type marked the course. In 1 case marked emotional instability was exhibited. In the remainder (5) there were no characteristic phenomena by which classification could be attempted.

CASE 4 (table 6).—M. R., a 36 year old housewife, had always enjoyed excellent health until the birth of her fourth baby. There was no history of hypertension in the family. At the age of 21 she was said to suffer from malaria. She had always been nervous and high strung and usually underweight. The first three pregnancies, at the ages of 22, 25 and 27, were normal; no rise in the blood pressure was noticed. At the age of 29, during the fourth pregnancy, the blood pressure became elevated during the seventh month, reaching a level of 228 systolic and 138 diastolic. The patient complained of no symptoms at this time, and delivery was normal. The urine was normal until delivery, but during the first two weeks post partum there were marked albuminuria and pyuria, both of which disappeared before her discharge from the hospital. Hypertension persisted, however, exhibiting the following course: At the age of 31 the systolic pressure was 260 and the diastolic 140, and at 33 the systolic pressure was 290 and the diastolic 160. At the age of 34 she had hemiplegia and became totally blind. The systolic pressure was 230 and the diastolic pressure 130. Although the paralysis gradually disappeared, she never recovered her sight. Severe headaches, from which she had suffered a few months before this, disappeared only to recur two years later. She was admitted to this hospital with headache as her only complaint.

Important physical findings were a systolic pressure of 300 and a diastolic pressure of 165, almost total blindness, some increase in the deep reflexes on the right side, with a possible Babinski reaction, slight thickening of the peripheral vessels, moderate enlargement of the liver and duplication of the first sound of the heart. In the ocular fundi there were papilledema, well marked perivasculitis, evidence of old and fresh hemorrhages and marked atrophy of the optic nerves. The urea clearance was 55 per cent of normal. The maximal specific gravity of the urine was 1.017. The systolic pressure varied between 300 and 180 and the diastolic between 165 and 110, falling slowly after therapy with sodium thiocyanate but rising to 242 systolic and 138 diastolic when this treatment was discontinued. Shortly after this, coma set in, from which she did not recover. She died at the age of 38. At autopsy there were observed cerebral hemorrhage, generalized arteriolosclerosis and arteriolosclerotic nephritis. The kidneys showed many local scars, thickly infiltrated with lymphocytes.

*Summary.*—Hypertension began during the seventh month of the fourth pregnancy, cerebral symptoms predominating. It is uncertain whether infection of the kidneys or some endocrine disturbance was present at the onset, although the former seems more likely. Classification could not be attempted without more knowledge of what was abnormal during pregnancy.

TABLE 6.—*Unclassified Hypertension* ##

| Case No. | Sex | Patient | Family† History | Age at Onset,§ Years | Duration,‖ Years | Symptoms¶ When First Seen | Average Extremes‡‡ of Blood Pressure, Mm. Hg | | Ocular Fundi** | | Progress†† | Present State§§ | Other Classifying Signs## | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Highest | Lowest | Arteriosclerosis | Hemorrhage or Exudate | | | | |
| **Onset with Pregnancy** | | | | | | | | | | | | | | |
| 1 | ♀ | B. A. | + | 23 | 4 | H | 240/160 | 180/120 | + | ++ | R | D-R | 0 | Emotional instability |
| 2 | ♀ | M. P. | 0 | 22 | 8 | 0 | 180/135 | 150/110 | 0 | 0 | 0 | L | 0 | |
| 3 | ♀ | D. L.† | 0 | 19 | 6 | H | 270/180 | 170/110 | + | ++ | R | D-R | 0 | Obesity |
| 4 | ♀ | M. R. | 0 | 29 | 7 | H-Ce | 260/160 | 220/120 | + | + | Ce | D-Ce | 0 | |
| **Malignant Course** | | | | | | | | | | | | | | |
| 5 | ♂ | J. A.† | 0 | 37 | 5 | H-C | 240/160 | 180/130 | 0 | 0 | C-Ce | D-C | 0 | |
| 6 | ♂ | P. M.† | 0 | 36 | 2 | H | 270/170 | 190/130 | +++ | + | Ce | D-Ce | II+IV+++ | |
| 7 | ♂ | R. M.† | 0 | <39 | > 2 | H-C-Ce | 260/170 | 210/140 | + | 0 | Ce | D-Ce | IV++ | |
| 8 | ♂ | I. G. | 0 | 44 | 6 | H-C | 260/150 | 180/120 | 0 | + | C | D-C | II++ | |
| 9 | ♂ | M. P. | 0 | 31 | 4 | H-C | 270/180 | 210/140 | + | +++ | C-R | D-C-R | II++IV+++ | |
| **Possibly Belonging to Groups** | | | | | | | | | | | | | | |
| 10 | ♂ | J. R. | 0 | 31 | 12 | H | 170/110 | 140/ 95 | ± | 0 | 0 | L | II+++ | Possibly diencephalic |
| 11 | ♀ | E. J. | 0 | 18 | 2 | H | 210/130 | 155/100 | 0 | 0 | 0 | L | II+++ | Possibly diencephalic; congenital heart disease; marked lumbar scoliosis |
| 12 | ♀ | M. A. | 0 | 19 | 2 | 0 | 210/140 | 195/130 | 0 | + | 0 | L | II++ | Possibly diencephalic; emotional instability |
| 13 | ♀ | J. S. | 0 | 35 | 11 | 0 | 240/130 | 210/115 | + | 0 | Ce | D-Ce | III++ | Obesity |
| 14 | ♂ | F. G. | + | 10 | 10 | 0 | 200/100 | 170/ 80 | 0 | 0 | 0 | L | III++ | Treated for pituitary dyscrasia at 12 |
| 15 | ♂ | M. M. | 0 | <41 | > 9 | 0 | 180/115 | 160/105 | ± | 0 | 0 | L | III++ | Marked obesity |
| **Miscellaneous** | | | | | | | | | | | | | | |
| 16 | ♀ | R. P. | 0 | 16 | 3 | 0 | 160/ 90 | 140/ 70 | 0 | 0 | 0 | L | II++II+ | Mild hypertension; obesity |
| 17 | ♂ | G. S. | 0 | 17 | 3 | 0 | 150/ 95 | 135/ 80 | 0 | 0 | 0 | L | II++ | Mild hypertension |
| 18 | ♂ | M. F. | 0 | 28 | 8 | H | 170/110 | 140/ 80 | 0 | 0 | 0 | L | 0 | Mild hypertension |
| 19 | ♂ | B. P. | 0 | 19 | 6 | H | 145/ 95 | 135/ 80 | 0 | 0 | 0 | L | III+ | Mild hypertension |
| 20 | ♂ | A. L. | 0 | 17 | 2 | 0 | 170/100 | 135/ 80 | 0 | 0 | 0 | L | II++ | Mild hypertension |
| 21 | ♂ | P. H. | 0 | 19 | 2 | 0 | 160/ 90 | 135/ 80 | 0 | 0 | 0 | L | II++ | Mild hypertension |
| 22 | ♀ | R. R. | + | 27 | 3 | H | 210/115 | 140/ 90 | 0 | 0 | 0 | L | II+ | Emotional instability |
| 23 | ♀ | M. M. | + | 36 | 7 | Ce | 260/145 | 200/120 | 0 | + | 0 | L | II+ | Unclassifiable |
| 24 | ♀ | B. G. | 0 | 24 | 2 | 0 | 270/170 | 220/150 | 0 | + | 0 | L | 0 | Unclassifiable |
| 25 | ♂ | J. K. | 0 | 20 | 18 | H-C | 200/135 | 150/130 | + | + | C | D-Ce | II++IV+ | Unclassifiable |
| 26 | ♀ | M. A. | + | 20 | 14 | H | 210/130 | 190/120 | ± | 0 | 0 | L | 0 | Unclassifiable |
| 27 | ♀ | F. C. | + | 25 | 2 | 0 | 210/130 | 180/120 | 0 | 0 | 0 | L | 0 | Unclassifiable |
| **Insufficient Data** | | | | | | | | | | | | | | |
| 28 | ♀ | N. W. | 0 | 52 | ? | H | 220/120 | 210/ 90 | ? | ? | ? | D-? | IV+++ | Moderate arteriosclerosis |
| 29 | ♂ | H. L. | 0 | <56 | ? | C | 210/110 | 180/100 | ? | ? | C | ? | 0 | |
| 30 | ♀ | A. M. | 0 | 50 | ? | C | 200/110 | 180/100 | ? | ? | ? | ? | IV+ | |
| 31 | ♀ | E. J. | 0 | 48 | ? | H | 240/160 | 230/140 | + | + | ? | ? | IV+ | |
| 32 | ♂ | E. W. | + | 29 | 1 | 0 | 250/150 | 200/130 | + | + | C-R | D-C-R | IV+ | |
| 33 | ♂ | A. O. | 0 | 39 | > 7 | H-C | 240/140 | 190/120 | ? | ? | ? | ? | IV++ | |
| 34 | ♀ | A. M. | 0 | 35 | > 7 | H | 240/160 | 190/130 | ++ | + | ? | ? | III++ | Obesity; menorrhagia |
| 35 | ♀ | E. V. | 0 | <39 | > 9 | H | 230/140 | 190/130 | + | + | Ce | D-? | IV++ | |
| 36 | ♀ | M. D. | + | <27 | > 2 | H-C | 200/140 | 180/125 | 0 | 0 | Ce | D-Ce | III+ | |
| 37 | ♂ | L. S. | 0 | 49 | > 5 | H | 240/140 | 185/110 | + | 0 | ? | ? | II++ | |
| | | | 19%+ | Average 30.4 yr. | Average 5.6 L 6.0 D | 59% H >29% C Ce | Average 217/131 | Average 178/111 | 33%+ | 42%+ | | 45% D (33% with renal failure) | | |

‡‡ For explanation of symbols and abbreviations, see footnotes to table 2.

COMMENT

Although "essential" hypertension has been regarded as a primary disease for a number of years, the question is raised again whether it is not merely a syndrome common to a number of maladies. If so, some or all of the contributing mechanisms would be better understood if viewed in association with coexistent disturbances. The adoption of this attitude has been useful in understanding and in classifying cases in which hypertension has been considered "essential" and in which the underlying abnormal processes have been unsuspected. The fact that these abnormal processes appear to be chiefly related to the four systems set forth in the classification simplifies the problem of discussion. Comments are made under the four main headings.

I. When renal failure is present, it is of course known that arterial hypertension may accompany many diseases of the kidneys. When in the absence of renal insufficiency arterial hypertension is associated with organic renal disease, it is naturally not known what part the renal lesion has played in bringing it about. Renal disease can be regarded as causally related to hypertension only in cases in which the diastolic pressure has fallen after removal of a diseased kidney.

Certain renal abnormalities seem, therefore, to occasion hypertension, although they occur also in its absence. Those now reported in cases in which hypertension has been considered "essential" cannot be shown conclusively to have caused it. However, the frequency with which renal abnormalities are found in such cases and the fact that their presence often antedates the elevation of blood pressure suggest that they bear some intimate relation to that elevation. In all events, the patients in this group are indistinguishable from those who have been regarded as suffering from "essential" hypertension except that 61 per cent of them have sustained some damage to their kidneys before the development of hypertension and the remainder exhibit signs of renal disease without failure, the nature of which is not usually believed to be associated with elevated arterial pressure. The condition is now designated "renal hypertension without failure."

The observations that a rapid course is not unusual (35 per cent), that hemorrhagic and exudative lesions of the retina are common (65 per cent) and that death from renal failure is often the outcome (76 per cent) suggest that cases of this type form a distinct group.

II. A different group is that in which arterial hypertension is exhibited along with the "hypertensive diencephalic syndrome." Although the evidence, experimental and clinical,[28] that the diencephalon is

28. Bard, P.: The Central Representation of the Sympathetic System as Indicated by Certain Physiologic Observations, Arch. Neurol. & Psychiat. **22**:230 (Aug.) 1929.

involved is indirect,[16] there is a preponderance of symptoms suggesting derangement of certain functions of the nervous system. There is further evidence indicating that these cases form a separate group: The arterial hypertension is benign. It occurs in younger persons and occasions few of the signs commonly associated with hypertension at this age. Changes in the retaina, cardiac enlargement and failure of renal function are unusual. The marked lability of the blood pressure is noteworthy, even if hypertension has been present for many years. The progress of the disease appears to be extremely slow even when the blood pressure is markedly elevated. Patients on whom section of the anterior spinal nerve roots has been performed have improved,[29] though the meaning of this improvement is not clear. On clinical grounds, therefore, this group appears to constitute a special variety of cases of "essential" hypertension. Because of the predominance of symptoms depending on disturbances of the nervous system, the hypertension is designated "nervous hypertension."

III. Although disturbances of the endocrine glands have sometimes been believed to be associated with "essential" hypertension, it is still not clear whether dysfunction of these organs can be responsible for elevation of arterial pressure except in cases of pronounced endocrine dyscrasia (e. g., cases of Cushing's syndrome). However, endocrine dysfunction of less pronounced form is undoubtedly associated with "essential" hypertension in some cases, being present in 19 per cent of ours and in many instances (51 per cent) appearing at the onset of the disease. We have called such a condition "endocrine hypertension."

The cases in this category exhibit clinical differences, although the complaint of severe headache is frequent. In cases of "nongoitrous thyrotoxic hypertension" the illness progresses rapidly, symptoms are severe, and hemorrhagic and exudative lesions are seen in the retina. In cases in which hypertension begins at the menopause it runs a benign course. The same is true in cases in which hypertension follows recovery from hyperthyroidism. While in 10 of 43 patients the course was consistent with the diagnosis of malignant hypertension, 13 have lived more than ten years.

IV. Arterial hypertension is now believed to follow lesions of the blood vessels only when these lesions involve the arteries supplying the kidney. In animals, elevation of the diastolic pressure can be produced by partial constriction of these arteries. In human beings a similar mechanism is believed to be operative when they are narrowed by arterio-

29. (*a*) Page, I. H.: Medical Aspects of Surgical Treatment of Hypertension, J. A. M. A. **110**:1161 (April 9) 1938. (*b*) Page, I. H., and Heuer, G. J.: Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots, Arch. Int. Med. **59**:245 (Feb.) 1937.

sclerosis (Goldblatt;[27] Leiter[10]). Hypertension occurring with periarteritis nodosa of the renal arteries and that occurring with coarctation of the aorta may depend on a similar defect. Whether narrowing of the *intrarenal* arteries by degenerative changes plays a part in the genesis of hypertension is still uncertain, although such changes are frequently seen in elderly persons.

Older patients with general arteriosclerosis and high diastolic pressure exhibit enough clinical uniformity for their cases to be regarded as belonging to a separate group. The justification for this suggestion consists of a lack of certain signs (such as exudative lesions in the retina) and symptoms (such as headache or palpitation) common in other cases and of the absence of renal lesions, of disturbances of the nervous system and of endocrine dysfunction. In addition, the course is usually benign (87 per cent); arteriosclerosis of the vessels of the retina (but not retinitis) is common (97 per cent); the terminal event is often apoplexy (64 per cent). We designate the hypertension shown in this group "arteriosclerotic hypertension."

No distinction has been made between so-called benign and malignant hypertension. It has been found impossible to place cases in which the course is rapidly downhill in a separate group, since most of them exhibit the same phenomena used in classifying cases in which the course is "benign." Further studies are necessary to learn whether these cases form a separate group.

This study suggests that "essential" hypertension is not a primary disease. The fact that this diagnosis is made by exclusion should indicate multiple causes. The differences found among groups of cases is evidence that many causes are possible. In too many instances the associated disturbances may be significant. The unity of "essential" hypertension is, therefore, seriously called into question. In the light of this recital the need for a new classification is obvious. The present classification cannot be regarded as more than tentative. It has already been of advantage in facilitating diagnosis, in making prognosis more accurate and in setting the indications for therapy on a more reasonable basis. It is desirable that other means of differentiation be utilized to establish what is "essential" in this condition.

## SUMMARY

Two hundred and eighteen cases of so-called "essential" hypertension have been studied and classified from the standpoint of the varied phenomena which have been observed. Five main groups have been tentatively distinguished on the basis of the criteria used: (1) renal; (2) nervous; (3) endocrine; (4) vascular, and (5) unclassified. These groups exhibit disorders in the same systems as do those in which secondary arterial hypertension is found.

# SHOCK

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The physician confronted with a gravely ill patient, pallid and cyanotic, with a rapid, hardly palpable pulse and frequent, shallow breathing, thinks of heart failure and injects digitalis. This procedure, however, is the right one in only part of the cases, for frequently the condition described has nothing to do with poor heart action. I must admit that I have made this mistake myself on several occasions. I have needed much time to realize how little is generally achieved by stimulation.

One must always consider whether the heart has caused this serious condition or whether the picture should be ascribed to peripheral circulatory failure. In the latter case one speaks of the shock syndrome. A precise knowledge of the symptoms will always enable the physician to differentiate the two conditions.

In medical literature and especially in common parlance there is much confusion about shock. Though I have chosen to term the clinical syndrome underlying peripheral circulatory failure shock, because this term is in general use with investigators in this field, others prefer to speak of collapse. Still others use both terms indiscriminately. Tendeloo differentiated between collapse, on the one hand, and psychic or traumatic shock on the other. Since, however, it can be demonstrated that both conditions have the same pathogenesis, it is erroneous to use these names as if they designated different conditions.

For a long time shock was known to the surgeon only as an effect of injury or operation. Romberg and Paezler were the first to introduce the concept of shock into the literature of internal medicine. They emphasized that the deterioration of the pulse in acute infectious diseases is generally a result not of heart failure but of peripheral circulatory weakness caused by vasomotor paralysis. During and after the great war much work was done on the pathogenesis of traumatic shock, and only then was it realized how frequently this syndrome occurs in all kinds of internal diseases. By shock I mean the clinical syndrome resulting from a discrepancy between the blood volume and the capacity of the vascular system.[1] All considerations on the subject must be regarded from this point of view.

1. Moon, V. H.: Ann. Int. Med. **8**:1633, 1935. Freeman, N. E.; Shaw, J. L., and Snyder, J. C.: J. Clin. Investigation **15**:651, 1936.

Under these circumstances the large veins are poorly filled, the heart receives too little blood, and the cardiac output becomes less. Accelerated heart action ensues in an attempt at compensation, but if the minute volume nevertheless decreases, a marked fall of the blood pressure is inevitable.

The considerable fall in blood pressure, the poorly filled large veins and the small heart figure are the principal landmarks that distinguish peripheral circulatory failure from heart failure. In the latter condition an important decrease of the blood pressure is rarely met with, and the dilated heart and engorged veins clearly point to a different condition.

### SYMPTOMS OF THE SHOCK SYNDROME [2]

The skin is pale. The lips, ears and nails are cyanotic. The body is cold and clammy, especially the nose, fingers and toes. Sometimes the skin is dry and its elasticity low; sometimes it is covered with drops of sweat, depending on the cause of the shock. Cutis marmorata is a sign of poor circulation and results from irregular filling of the subpapillary venous plexus. The rectal temperature is often lowered, but there may be pyrexia in spite of the coldness of the skin.

The patients prefer lying flat in bed, in contrast to patients with cardiac disease, most of whom suffer from orthopnea. The cheeks are sunken; the eyes lie deep. The description corresponds to facies hippocratica; in fact, in peritonitis the shock syndrome is often outstanding.

Consciousness is variously influenced. Some of the patients are apathetic, do not reply to questions and hardly react to stimuli. Therefore, these patients do not complain of the violent pain that may have caused the shock (coronary occlusion, injury). Others, however, are conscious to the very end, replying to questions in a hardly audible voice but correctly. Still others are restless and exalted and want to leave their beds.

I recently saw a patient in profound shock due to gastric hemorrhage. He was unreasonable; he screamed and could be kept under control only with much difficulty during the blood transfusion, which was carried out with all speed. During the transfusion the pulse improved, the skin became warm, and the restlessness disappeared. Bleeding patients who become restless in this way require the utmost care. They may be in shock, and when given morphine they may die unnoticed. The patients complain of thirst. When given a drink, they vomit, the vomitus being often mixed with blood. During the shock of diabetic coma I have repeatedly seen the typical brown vomitus of hemorrhage by diapedesis.

2. Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937.

Respiration is usually shallow and rapid with occasional deep sighing. On a few occasions I have observed Cheyne-Stokes and Kussmaul respiration.

The pulse is rapid and soft. Often its rate increases, sometimes to 160 or 180. Not infrequently the pulse is impalpable.

The blood pressure is generally much decreased. This applies to both the maximal and the minimal pressure. Sometimes the blood pressure can be measured only by palpation. The maximal value (systolic) is often below 70 mm. of mercury. The tachycardia is probably a response to the low aortic pressure. When one succeeds in bringing the blood pressure to a suitable level by infusion, one finds that the pulse rate falls almost simultaneously. At the onset of shock the blood pressure is sometimes temporarily raised; the compensatory contraction of the arteries as a result of the lowering of blood volume may be intense. (This rapid and marked fall of the blood pressure is never found in heart failure. In that condition the blood pressure is in general normal or raised, and not before the agonal stage is it seen to decrease.)

The heart can be delimited by percussion with difficulty. When under these conditions a roentgenogram is taken, the heart is found to be very small. The cardiac sounds are soft; the second sound because of the low blood pressure, the first because the muscular sound is weak, owing to the low cardiac output. Thus a sensation of embryocardia can be obtained.

The superficial veins are collapsed, which becomes obvious on attempts at venipuncture. The pressure in the vein may even be below 1 to 2 cm of water.

The reflexes are low. The pupils are dilated and react defectively to light.

The urinary output is generally low. Occasionally I have seen anuria develop. The specific gravity of the urine, in contrast to that in cases of circulatory congestion is usually low. Sometimes typical isosthenuria is observed. The poor renal function, as well as extrarenal factors, leads to uremia. Renal failure must be ascribed to the lessened flow of blood through the kidneys, with anoxemia supervening. The kidneys are severely damaged, since their function requires much oxygen. This is comparable with the renal insufficiency of severe anemia.

Diuresis is much lowered when shock is attended by dehydration due to vomiting and diarrhea. The extrarenal factors causing uremia are dehydration, fever and autolysis. The blood often shows a loss of chlorides and bases (sodium). Generally there is acidosis. I have often found values for alkali reserve between 20 and 30 volumes per cent. The causes of acidosis are manifold. Owing to the anoxemia,

intermediary metabolites are incompletely oxidated. The resynthesis from lactic acid is decreased, which causes the lactic acid content to rise. At venipuncture the dark color of the blood is always conspicuous. On analysis the oxygen content is found to be below normal. This is due to the fact that the slow blood stream gives off much of its oxygen. Yet the tissues receive too little oxygen.

The temperature is lowered as the production of heat becomes defective through slowing of the blood stream, and the fall in temperature is enhanced by the accelerated breathing and sweating. On account of its slow current the blood cools excessively.

I have repeatedly emphasized that the heart is not the cause of this condition. The heart in failure is always dilated, except in paroxysmal tachycardia and concretio cordis. Another circumstance which shows the heart to be healthy in shock is that when one replenishes the decreased blood volume by infusion one often has to use several liters of fluid before the blood pressure is reestablished. It is found that the heart can stand this extra burden without damage. I do not think one can load the circulation with so much fluid with impunity if the heart is diseased. At autopsy, however, the heart is often observed to be flabby and dilated. This observation has checked the development of knowledge of shock for a long time. During life the heart is found on roentgen examination to be small. Probably it is dilated shortly before death, when it succumbs to the damage caused by poor circulation.

It is remarkable that a number of quite different diseases can all lead to the identical, sharply outlined syndrome of shock. Among the causative factors may be mentioned hemorrhage, acute infective diseases, poisoning, injury, pain, emotion, operations, loss of fluid by vomiting and diarrhea, perforation of abdominal viscera, pancreatitis, peritonitis, pulmonary edema, coronary thrombosis, pulmonary embolism, burns, congelation, hyperthermia, anaphylaxis, diabetic coma and Addison's disease.

## PATHOGENESIS [3]

All these conditions must have one factor in common, which leads to the shock syndrome. This common factor is the discrepancy occurring in all these conditions between the blood volume and the capacity of the vascular system. This discrepancy may occur in any of three ways:

1. By a decrease of the blood volume.
2. By an increase of the vascular capacity.
3. By a combination of these factors.

A decrease of blood volume in its simplest form is caused by serious loss of blood, of the kind most commonly observed in cases of bleeding

3. Wiggers, C. J.: Physiology in Health and Disease, ed. 2, Philadelphia, W. B. Saunders Company, 1937.

peptic ulcer. The shock caused by such a decrease is by far the easiest to understand and is most simply mended by blood transfusion. A decrease of blood volume may also be the result of dehydration. The loss of fluid may be due to severe vomiting or diarrhea or to intense polyuria, as in diabetes. In examination of the blood dehydration manifests itself by a high hemoglobin content, a high red cell count, a high cell volume in the hematocrit and a raised level of plasma protein. The concentration of the blood may increase by 20 to 50 per cent.

Loss of fluid may be brought about in still another way. Cases of shock are frequently observed in which the circulating blood volume is decreased by exudation of plasma. Harkins [4] spoke of "plasma-exudation"; Eppinger,[5] of *seröse Entzündung.* When this occurs there is concentration of the corpuscular elements of the blood (hemoglobin content, red cell count and hematocrit value are high), but with a normal level of plasma protein. A quantity of plasma must have escaped from the circulatory system. Eppinger was able to prove this by demonstrating an increased production of lymph in animals in histamin shock.

*A.* Decreased blood volume
  1. Loss of blood: normal blood constituents
  2. Dehydration: high values for protein and hemoglobin
  3. Loss of plasma: high values for hemoglobin and normal values for protein

*B.* Increased vascular capacity
  1. Central (vasomotor paralysis)
  2. Peripheral (vascular poisons)

*C.* *A* and *B* combined

This is easily understood in cases of peritonitis, pulmonary edema, war gas poisoning, combustion and freezing (Harkins). Blalock [6] was able to demonstrate that contusion, combustion and freezing of a limb caused a considerable increase in its weight as compared with that of the untreated limb.

Shock may be brought about by general damage to the capillaries. This is probably the explanation of traumatic shock (Moon). Substances are absorbed from the injured area which damage the capillaries. This has been proved experimentally. When an extremity of an animal is crushed, no shock follows if the femoral vein is ligated. As soon, however, as the ligature is released, symptoms of shock appear. Furthermore, aqueous extracts have been derived from the injured tissues which when injected into the blood stream of animals cause shock.

4. Harkins, H. N.: Ann. Surg. **102**:444, 1935. Harkins, H. N., and Harmon, P. H.: ibid. **106**:1070, 1937.

5. Eppinger, H.; Kaunitz, H., and Popper, H.: Die seröse Entzündung: Eine Permeabilitäts-Pathologie, Berlin, Julius Springer, 1935.

6. Harrison, W. G., Jr., and Blalock, A.: Ann. Surg. **96**:36, 1932.

In all such cases high values for hemoglobin are found, with a normal protein content. Probably histamine-like substances are in play, which are known to be formed in destruction of tissue. In fact, the best way of studying shock experimentally is by injection of histamine into animals. Shock can be produced experimentally also by implantation of living or injured tissue in the abdominal cavity.

The post mortem observation in cases of death from traumatic shock completely correspond with the findings in experimental shock; the peripheral veins are empty, the viscera are swollen and deep red and the small venules and capillaries of the viscera are engorged. There is blood-stained exudate in the body cavities. The mucous membranes of the thoracic and abdominal organs are red and swollen. Numerous hemorrhages are observed, and when the course has not been too rapid there is pulmonary edema. Taken together, these observations point to a loss of tone of the smaller vessels and to extravasation of plasma—changes which one knows as effects of vascular poisons. The same picture is observed in patients who have died in shock from acute infective disease, after injections of gold compounds (Heubner), and in poisoning by mercury (McNider), alcohol, ethyl carbamate (urethane) or barbital. Peptone, albumose, histamine, bacteria or bacterial toxins may also be the cause.

Even in cases of combustion and war gas poisoning, however, there is, in addition to local exudation of plasma, general damage to the capillaries, which causes depletion of the blood volume.

Not only decrease of blood volume but increase of vascular capacity may be the cause of the discrepancy. Under normal conditions only part of the capillaries are patent at the same time. If all the capillaries of the skeletal muscle system opened simultaneously, they could easily contain the whole blood volume (Krogh). Under certain circumstances the capillaries do not respond to the stimuli that should make them contract; thus they withdraw the blood from the circulation just as a sponge absorbs water. In this way the volume of the vascular system is considerably augmented. Dale proved that histamine, among other substances, brings about such vascular atony. It causes the capillaries and venules to become dilated and crammed with blood. With the dilatation there is increase in the permeability of these vessels, resulting in concentration of the blood and edema of the tissues. Part of the blood, therefore, may be stored in the skin (cutis marmorata). Blood obtained from the capillaries of the skin by pricking the finger shows a considerably higher red cell count than does blood derived from the cubital vein. It is clear, therefore, that shock in many cases is due to a combination of the two factors mentioned, i. e., decreased blood volume and increased vascular capacity. In the dilated capillaries the blood flows slowly or not at all and is thus withdrawn from the circulation. In determinations of the circulating blood volume by

the congo red method the stain does not mix with this stagnant blood, so that a reduced blood volume is found, and, in fact, this is practically the cause. The patient is said to bleed to death in his own vessels. Whether the blood volume is reduced by hemorrhage, by loss of plasma or by withdrawal of a portion of the blood from the circulation, the result is practically the same.

### ASSOCIATION OF SHOCK WITH VARIOUS CONDITIONS

*Trauma.*—During the war shock was seen to develop immediately after injury or after a lapse of hours (up to twenty-four). Ordinarily under these conditions shock was called primary and secondary. It was often observed that the late onset of shock coincided with a long-lasting transport, which added the factor of cold to the agents reducing the volume of circulating blood.

Primary traumatic shock develops suddenly, immediately following physical or mental injury. The sudden onset suggests that the nervous system plays an important part. Primary shock may result also from stimulation of the vagus nerve or from paralysis referable to the sympathetic nerves. Lewis referred mainly to vagal stimulation in his description of vasovagal syncope, in which low blood pressure accompanies slowing of the pulse. This description corresponds with Tendeloo's concept of shock. Abdominal operations may cause a sudden fall of the blood pressure, with slowing of the pulse. This is also ascribed to vagal stimulation. Epinephrine immediately relieves the condition. This type of shock Phemister and Livingstone saw in 17[7] of 175 gastric operations and in 29 of 209 operations on the gallbladder. With nitrous oxide anesthesia this type of shock is rarely encountered. Primary shock is seen also in cases of perforation of abdominal viscera after an injury to the abdomen or the testicles. This process has been compared to Goltz's experiment, in which vasodilatation of the splanchnic area is brought about by repeated tapping on the abdomen. In this instance also the blood accumulates in the abdominal vessels. Paralysis referable to the sympathetic nerves can also give rise to shock, for instance, paralysis produced by a lesion of the cervical portion of the spine or by spinal anesthesia. In this form of primary shock the circulating blood volume is reduced by stagnation, but the blood is not concentrated. Yet it remains questionable whether this explanation holds for all types of primary shock, as several surgeons have assured me that they have not observed the engorgement of the abdominal vessels which should result. Besides, experiments are on record in which stimulation of the abdominal portion of the vagus nerve led to a rise of the blood pressure. It is a difficult field of investigation, as the patients either recover from primary shock rapidly or die rapidly.

7. Phemister, D. B., and Livingstone, H.: Ann. Surg. **100**:714, 1934.

Secondary shock develops later and in general is much more serious. The aforementioned considerations of Moon make it probable that generalized toxic damage to the capillaries is in play. In this form of shock the reduction in circulating blood volume is constant. The more severe the shock, the greater the reduction. A decrease of 85 per cent has been observed.

For a long time the opinion has prevailed that traumatic shock is caused by vasomotor paralysis. It has, however, been shown repeatedly that the vasomotor system well retains its excitability for carbon dioxide. The pale skin also demonstrates arterial spasm, which is hardly consistent with reduced vasomotor activity. The picture rather suggests that the vasomotor center responds well, for the contraction of the cutaneous vessels may warrant a sufficient blood supply to the brain and heart for a long time.

The probable causes of traumatic shock are generalized dilatation of the visceral capillaries with exudation of plasma and local dilatation with extravasation of blood and plasma in the injured parts.

*Postoperative Conditions.*[8]—Shock occurring after surgical intervention is ascribed to the same factors. Histamine-like substances should likewise be released into the blood stream. There are a lowered venous pressure and a reduced blood volume. Handling of the intestines is said to lead to the extravasation of much plasma (Blalock). The factor of dehydration should not be lost sight of, being a factor common to all operations.

"Purging" of the patient, restraint on the fluid intake and loss of water by deep respiration are factors not to be underrated.

*Loss of Blood.*—Shock due to this condition is easiest to explain. Much depends on the quantity of the hemorrhage and the speed of the bleeding. When a patient with gastric hemorrhage succumbs, it is the result of shock. Treatment, therefore, should be directed against shock by refilling the vascular system. In cases of serious involvement I resort not to simple blood transfusion but to intravenous drip infusion, which permits continuous administration of the fluid, the volume being controlled under guidance of the pulse and blood pressure. One may make a choice among various fluids—blood, Bayliss' fluid [8a] or Ringer's solution. I think that this method represents progress in the treatment of life-endangering hemorrhage. Statistics showing mortality reduced under this treatment do not tell much; the fact that I have succeeded in rescuing patients in deep shock, pulseless and with no measurable blood pressure, is a more valuable testimony.

8. Mann, F. C., and Essex, H. E.: The Present Status of the Problem of Traumatic Shock, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1935, vol. 27, p. 1231.

8a. Bayliss' fluid consists of 60 gm. of acacia, 9 gm. of sodium chloride and 1,000 gm. of distilled water.

*Acute Infectious Diseases.*—Shock is frequently observed in the course of infections. Except in rheumatic fever and diphtheria, a disturbance of circulation in the course of an infection is generally not caused by the heart. This type of shock has been well investigated by Romberg and Paeszler. They supposed the cause to be vasodilatation due to vasomotor paralysis. Further investigations by means of animal experiments have shown that the lowered excitability of the vasomotor centers is a result rather than a cause of the shock.

During an epidemic of influenza in 1920 Underhill and Ringer[9] found shock with marked concentration of the blood (hemoglobin content 140) in the cases in which the outcome was fatal. They compared this condition with what they had seen in cases of phosgene poisoning, noting, however, that in the latter the picture developed in hours, whereas in the cases of influenza days were required. In both types of cases there were pulmonary edema and intense hemoconcentration. The latter sign, however, is far from constantly found in cases of acute infectious diseases in which shock has developed. It is my experience that in most cases it is not present. In January 1937 I had an opportunity of examining closely a number of patients with influenza who died in shock. In spite of a complete and distinct picture of shock, with a blood pressure of 50 to 60 mm., a hardly palpable pulse and empty veins, these conditions generally persisting for several days, I never found a rise in the red cell count or in the cell volume. My experience with shock in patients suffering from other acute infective diseases, particularly in a number of patients with pneumonia and scarlet fever, is of the same kind; there was no concentration of the blood even to the ultimate stage. Recently a man suffering from tropical malaria was admitted to the hospital in deep shock. He died an hour later, and there was no concentration of the blood. I do not know how to explain shock in such cases. The great resemblance to traumatic shock, in which there is certainly a reduced blood volume, makes it probable that in these cases also toxins are in play, acting peripherally on the capillaries and causing dilatation with or without extravasation of plasma. I have never succeeded in saving a patient in severe shock from infectious disease.

*Poisoning.*—In various kinds of poisoning the shock syndrome may be studied. I have observed it in veronal (barbital), mercury bichloride, arsenic and oxalic acid poisoning. In war gas poisoning, especially, shock develops extremely rapidly, and the management of this poisoning is mainly the treatment of shock. A patient who had taken about 13 Gm. of arsenic acid was admitted to the hospital five hours later. He was in typical shock. The pulse could not be felt, nor could the blood

9. Underhill, F. P., and Ringer, M.: Blood Concentration Changes in Influenza, with Suggestions for Treatment, J. A. M. A. **75**:1531 (Dec. 4) 1920.

pressure be determined. The erythrocyte count was 7,000,000 per cubic millimeter. An intravenous drip temporarily raised the blood pressure to 80 mm. systolic, and the circulation improved. The success, however, was transitory, as the patient died with the signs of pulmonary edema.

*Vomiting and Diarrhea.*—Here the supervening of shock is easily understood when one realizes how much fluid may be lost by the patient. Not only the tissues but the blood is dehydrated. The picture of dehydration and concentration of blood may be striking. Loss of salt and uremia also develop, but these are secondary symptoms. The danger lies in a reduction of the blood volume incompatible with life. In recent years much has been written about "extrarenal uremia," caused by dehydration on loss of salt. Yet I do not think that in this case the danger comes from uremia. The menace should be sought rather in the reduction of circulating blood volume. Treatment should be directed to combating dehydration by means of fluid or salt. By these means shock is abolished, and uremia disappears as the circulation improves. This form of shock is amenable to therapeutic intervention. Fluid up to several liters is often required for replenishing the loss, the red cell count being a practical means of estimating the dose. When one realizes that up to 7 liters a day has been given in these conditions, partly intravenously, one understands that good cardiac function must have been present. I observed severe shock in a few cases of paratyphoid fever with severe diarrhea. One patient with paratyphoid B died in deep shock after an illness of twenty-four hours. The red cell volume was 60 per cent, the plasma volume only 40 per cent. The red cell count was 9,000,000 per cubic millimeter. Treatment was incapable of permanently filling the vascular system; the fluid administered actually left the vessels at the same rate, for the red cell count remained the same. A serious danger of shock which continues for a long time is anuria, which may become irreversible. I have observed this on a few occasions, once in a patient with diabetes, once in a patient with paratyphoid B. In both patients autopsy revealed nephrosis.

I saw a patient with paratyphoid B who had had severe diarrhea for two days. On admission there was severe shock. The skin was cyanotic, cold and moist. The patient had the hippocratic facies and did not respond to stimuli. His pulse rate was 160 to 170; his systolic blood pressure was 60 mm. On venipuncture I was struck by the treacly consistency of the blood. The hemoglobin level was 150 per cent, the red cell count 8,000,000 per cubic millimeter, the protein content of the plasma 6.72 per cent, the blood urea 2 Gm. per liter and the alkali reserve 23 volumes per cent. On roentgen examination the heart was found very small. So I was dealing with shock from loss of plasma through the intestinal lesions. Intravenous drip treatment was instituted with the utmost speed. Two liters was introduced in two hours. The pulse became more easily palpable and the blood pressure rose to 90 mm. systolic. The skin became warm and less cyanotic. Acidosis was combated with sodium bicarbonate. The man recovered his speech

and gave the impression of having substantially improved. After the drip infusion was stopped the blood pressure fell again to 60 mm. The drip infusion was maintained for three days, the blood pressure rising to 120 systolic and 80 diastolic. The red cell count fell to 5,200,000 per cubic millimeter. The patient seemed well. It appeared, however, that only 40 to 60 cc. of urine was excreted. Intense albuminuria developed, and the man died, the urea content of the blood being 5.5 Gm. per liter. The pathologist observed nephrosis.

*Diabetes.*[10]—The prognosis of diabetic coma depends on several factors. Prior to the introduction of insulin coma was an entirely hopeless condition, and even now it is serious, though fortunately there is today a possibility of saving the patient's life. On studying larger statistics one finds that the mortality from diabetic coma, in spite of expert insulin treatment, is still high. When one ascertains the kind of cases in which insulin has not the desired effect, various causes can be found to account for this circumstance. One of these causes is shock. I shall give an illustrative instance.

Five years ago, in the evening, a boy aged 15 was admitted to the department in deep coma. He had been unconscious for about four hours; the cause of the coma had been the omission of the necessary dose of insulin. There was no history of infection. With massive doses of insulin I succeeded toward midnight in getting the boy to "come around;" the blood sugar had decreased considerably, and the alkali reserve had risen satisfactorily. The pulse was of good quality. Everything seemed favorable until, a few hours later, I was warned that the pulse was becoming poor. When I saw the boy the pulse could no longer be felt, and in a short time he died. At autopsy no explanation could be found for the sudden death.

Such a case, of course, did not fail to make a deep impression, especially as everything at first seemed to proceed well. This is, unfortunately, not the only instance I might cite. Now consider the way in which such an event can come about.

I then thought that the patient had collapsed suddenly. Later I became convinced of a more gradual development of such circulatory failure, which makes it possible to foresee the impending mischief by regularly observing the pulse and especially the systolic blood pressure. This value, which in diabetic coma is generally already low, gradually falls, attains a level of 80 to 70 to 60 mm. and eventually becomes undeterminable.

If one regularly determines the red cell count in diabetic coma, one will nearly always find marked hyperglobulia. Moreover, by certain

10. Lawrence, R. D.: Brit. M. J. **1**:690, 1930. Lande, H.: Uncontrollable Causes of Death in Diabetic Coma, J. A. M. A. **101**:9 (July 1) 1933. Labbé, M., and Boulin, R.: Presse méd. **41**:1705, 1933. Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1930, vol. 18, p. 634. Drabkin, D. L., and Edwards, D. J.: Am. J. Physiol. **70**:273, 1924. Drabkin, D. L., and Shilkret, H.: ibid. **83**:141, 1927.

methods based on the injection of dyes, one can demonstrate that the blood volume has actually decreased. The vascular system adapts itself as long as possible to the reduced blood volume, but if this diminishes too far the blood pressure will fall alarmingly. The cause of the concentration of the blood in diabetic coma is easily understood when one realizes that the patients always have considerable polyuria, and the loss of fluid is not compensated by drinking after the patient loses consciousness. Besides, if fluid can be taken, it is returned by vomiting. In spite of the serious dangers inherent in shock, one is not entirely powerless as to its treatment. As in so many chapters of clinical medicine, the rule holds that the most rapid intervention gives the best chance. What one is to do is obvious. Besides giving massive doses of insulin, one must apply measures to combat dehydration. I have adopted the rule of immediately administering 2 liters of physiologic solution of sodium chloride subcutaneously in every case of diabetic coma and, if necessary, repeating this procedure after a few hours. As soon as the patient can drink and does not vomit, I give fluids by mouth also. Meanwhile I carefully observe the blood pressure, which is read every half hour or even more frequently. When it falls, no profit will result from giving digitalis or other cardiac stimulants. One must try to raise the circulating blood volume in order to improve the diastolic filling of the heart and thus enable the heart to restore the blood pressure to normal levels. When in diabetic coma the blood pressure is very low, the blood sugar and the alkali reserve do not give a true picture of the condition. An immediate improvement, however, may result if one succeeds in raising the blood volume. I shall present an instance of shock associated with diabetic coma in which I succeeded in changing the condition for the better.

A girl aged 18 years was admitted unconscious to the department at 7 p. m. on June 20, 1934. She showed the typical picture of diabetic coma. The face was highly flushed; the respiration was of the "large" type. The maximal blood pressure was 120 mm. and the minimal 75 mm. The blood sugar amounted to 514 mg. per hundred cubic centimeters and the alkali reserve to 16 volumes per cent. The blood was distinctly concentrated, the red cell count being 6,000,000 per cubic millimeter. Immediately 100 units of insulin was injected. Two hours later the value for blood sugar had fallen to 375 mg. per hundred cubic centimeters. Again 50 units were given. At 11 p. m. the blood pressure became lower; at midnight the pulse was hardly perceptible. The value for blood sugar at that time was 170 mg. per hundred cubic centimeters. The picture of coma had now completely changed. The girl was still unconscious; her color was no longer red but pale and cyanotic. The respiration, instead of being deep and slow, had become rapid and shallow. The heart, on percussion, was not enlarged. The skin was cold, and the condition appeared alarming. Intravenous infusion was decided on. This was not easy, as the veins were so collapsed that I did not succeed in carrying out venipuncture. A vein had to be dissected free, after which a slow infusion of Bayliss' fluid was given. The pulse gradually became palpable. When 600 cc. had been given, the blood pressure measured 150 systolic

and 80 diastolic. Epinephrine (1 mg.) had been added to the fluid. The skin felt warm, and disappearance of the pallor and cyanosis was a further sign of an improved circulation. The condition at one stroke had changed for the better. Fortunately the improvement maintained itself, the blood pressure fell somewhat but remained within the limits of normal, and after a short time the patient spoke. She made a complete recovery. This girl's life was saved by refilling the vascular system and thereby restoring the circulation in good time.

I have not always succeeded in combating shock by restoring the blood volume with fluid and epinephrine. In the less favorable cases the infusion had a temporary effect, estimations showing the concentrated condition of the blood to have disappeared and the blood pressure to be reestablished, but after a few hours the values were seen to verge toward the alarming again. The quantity of urine produced during shock is generally small, which led me to assume that the fluid leaves the vessels and enters the tissues. At autopsy this is observed to be true, the organs being crammed with fluid. I recently observed such a case of shock, in which the fluid had drained from the vascular system. At autopsy the high fluid content of the abdominal viscera, lungs and subcutaneous fat was conspicuous. From the cut surface of the liver a pool of serous fluid collected in a short time.

The temporary nature of the effect of infusion of fluid might be ascribed to a too short duration of the effect of epinephrine. It is therefore certainly better to administer an intravenous drip infusion. At first until the pulse has improved, one may infuse rather rapidly, reducing the rate of the inflow to, say, 100 cc. of fluid an hour, with 0.2 per cent of epinephrine solution. This is continued until the blood pressure shows no more tendency to fall. It may be necessary to maintain the drip infusion for a few days at a stretch, regulating the rate of inflow as required and taking the blood pressure as a guide.

Recently I saw a young man who had come under the treatment of his family physician only the day before. The physician asked for his admission to the hospital because of glycosuria. The same night the condition became worse, and on admission the next morning the patient was in deep shock (impalpable pulse, unmeasurable blood pressure, empty veins). Had he been treated only with insulin, he would surely not have lived much longer. An intravenous drip infusion pulled him through. Two hours later his blood pressure was normal, and the danger of shock was overcome. Meanwhile the acidosis was combated successfully with insulin.

Shock in diabetic coma does not always develop at the height of the comatose condition. It may develop after the patient has regained full consciousness, so that he falls back into coma. Several authors have even reported that shock may develop a few days after the patient has recovered from coma. I never saw this happen, but the possibility being recognized, careful observation of the pulse and blood pressure even when everything seems well is necessary for days. Apart from frank

coma, severe diabetic acidosis without impairment of consciousness may also lead to shock. In this connection I wish to mention the case of a little boy who, ambulatory, came to the clinic with entirely unimpaired sensorium but with a high blood sugar and a low alkali reserve. The blood was highly concentrated and the blood pressure low. I immediately admitted the boy to the inpatient ward and treated him with large doses of insulin. Five hours later typical shock developed, after the value for blood sugar had become normal and the alkali reserve had risen satisfactorily. The boy had been given 500 units of insulin.

The genesis of shock in diabetes is still unexplained. Probably the acidosis itself is not responsible, for shock is repeatedly seen to develop after ketosis has diminished or even after the ketone bodies have disappeared from the blood and urine. I have often been struck by the fact that in spite of clinical treatment the pulse may become steadily more rapid and weak and the blood pressure fall. It is remarkable that this should happen after admission of the patient to the ward, when one would expect the condition to improve as a result of the better management under which the patient is placed. The disturbance of metabolism is dealt with by massive doses of insulin. Why, then, does shock develop?

There is some reason to suspect that the insulin is responsible for this. It is well known that injections of insulin, both in healthy and in diabetic persons, at first may lead to a marked increase in weight. This increase is caused by retention of water in the tissues. Edema may develop not from renal insufficiency but from purely extrarenal causes. In many diabetic persons one sees slight to moderate inspissation of the blood after the first injections of insulin. Under the action of insulin, water and salts leave the blood stream and are absorbed in the tissues. This, at least, is found during the first few hours or, at most, days of the insulin cure. Later, after the tissues have become saturated with fluid, the concentrated state of the blood disappears and even gives way to dilution. Thus some kind of balance is established. The concentration of the blood is more marked as the diabetes is more severe, the doses of insulin higher and the fall of the value for blood sugar more steep.

The concentration of the blood is most marked in hypoglycemic shock. Drabkin has proved this in experiments on dogs. I had an opportunity of examining schizophrenic patients during insulin shock induced therapeutically. I observed an increase of concentration of the blood, which could be shown by a rise of the protein content of the plasma and the red cell count. On one occasion I even saw the latter rise in a few hours from 4,900,000 to 6,300,000 per cubic millimeter. Drabkin was able to prove with dogs that the concentration of the blood was much more marked when the animals had previously

been brought into a state of dehydration by withdrawal of fluid from their diet. This evidence perhaps explains to some degree the development of shock in my diabetic patients. By the action of insulin the capillaries become permeable to water, the circulating blood volume decreases, the blood pressure falls and the previously described condition of shock is produced.

Schittenhelm in 1927 drew attention to the remarkable difference between patients who died in diabetic coma in the period before insulin came into use and those who now die from this cause after having been treated with insulin. Formerly, intense polyuria persisted to the last, whereas now anuria is conspicuous. This observation must be true. I have repeatedly observed patients admitted to the ward with full bladders, in whom, afterward, severe oliguria or even anuria developed. Probably both anuria and shock are the result of loss of fluid from the capillaries.

If it is true that insulin produces or perhaps aggravates shock, this is distressing, but for the present there is no means of preventing it with certainty. One can only urge physicians to be careful in giving large doses of insulin at once, if not strictly necessary. In treating a patient for fully developed coma the administration of large doses of insulin cannot be dispensed with; in treating for precoma, which is not such an emergency, it is better to give small hourly doses instead of larger doses at longer intervals. Under these conditions protamine zinc insulin may be valuable. It has been shown experimentally that this careful administration of insulin gives less rise to increased permeability of the vessel walls. It seems important, therefore, not to let the blood sugar level fall too rapidly. It can safely be left high, and the administration of sugar in case of a marked fall (perhaps even at the onset of treatment) will help in preventing shock. In clearcut diabetic coma, in which there is no time to lose, careful dosage may not be ventured. One must try as soon as possible to mend the state of dehydration by compensating for the loss of fluid from the vascular system in every accessible way. Regularly repeated counts of the erythrocytes indicate the progress of the dehydration, but the most important measure, in my opinion, is regular observation of the blood pressure. If it is very low or falls during treatment, one must not delay but must attempt to refill the vascular system.

Fatal shock in diabetic coma is more frequent in elderly persons than in the young. An analogous behavior is seen in severe gastric hemorrhage, which in elderly persons with arteriosclerosis is more dangerous than in subjects with healthy vessels. It is possible that this is due to the fact that a heart with narrow coronary vessels is more susceptible to a too low blood pressure than a normally vascularized heart.

*Addison's Disease.*—In Addison's disease, together with a low arterial pressure, a normal venous pressure is found. During the crises, however, the arterial pressure is reduced still further, and the venous pressure also falls. In adrenalectomized animals the circulating blood volume is considerably reduced. An extract of adrenal cortex may abolish this shock. During the crises in clinical cases I have also repeatedly observed a raised red cell count (up to 7,000,000) and a raised level of plasma protein. This condition can generally be adequately dealt with by the use of an extract of adrenal cortex alone. Fluid is of no use, as it leaves the vascular system. It is probable, therefore, that in adrenal failure the mechanism that keeps the quantity of circulating blood on a constant level is disturbed. This disturbance probably should be ascribed to loss of sodium, which in adrenal insufficiency is eliminated through the kidneys, carrying water with it. The sodium also escapes into the tissues, together with water. An extract of adrenal cortex can repair this disturbed regulation of the distribution of fluid between blood and tissues. The shock associated with adrenal failure is so well understood that the deduction has been drawn that in other forms of shock adrenal failure should be assumed. It is questionable, however, whether the similarity of the syndromes should induce one to assume a similarity of causes. If extract of adrenal cortex can bring about improvement in cases of shock of other types, this is no proof that adrenal failure is in play in all kinds of shock. Heuer and Andres studied shock occurring in animals after injection of extracts of putrefying intestinal contents. They found the typical picture of shock, with concentration of blood and extravasation of plasma. On injecting fluid they obtained no improvement, the fluid leaving the vessels. When they gave extract of adrenal cortex simultaneously with the fluid, good results were obtained, the blood pressure and plasma volume becoming normal. This does not necessarily mean that the shock brought about by these investigators was due to adrenal failure. I have repeatedly met with patients for whom the infusion of fluids was of no avail, the blood pressure remaining low and the concentration of the blood being little influenced. This shows only that the vessels are damaged to such a degree that the fluid drains away through their walls. I have therefore tried to give substances reducing the permeability of the vessel walls. Calcium, parathyroid extract and dihydrotachysterol (A. T. 10) were tried, without the least benefit. Success was often obtained by adding epinephrine, paramethylaminoethanolphenol tartrate (sympatol) or ephedrine to the fluid. It is possible that constriction of the vessels reduces their permeability. On a few occasions, however, I have seen good results from the use of an extract of adrenal cortex. This was true in the case of a patient in anaphylactic shock, who was given an intravenous drip infusion and

did not respond in spite of large quantities of fluid and epinephrine. Whether post hoc or propter hoc, administration of an extract of adrenal cortex was followed by improvement. The similarity of shock and adrenal crisis may be such that mistakes can be made.

Five years ago my advice was asked for a woman who had been admitted to the surgical department because of a condition diagnosed as ileus. She had a rapid pulse and a blood pressure of 70 to 80. Her skin was distinctly pigmented. I did not hesitate to make a diagnosis of Addison's disease. Uremia (blood urea 7 Gm. per liter) was present, but I did not consider this an uncommon feature, as the patient had vomited a great deal. After an initial improvement under the influence of extract of adrenal cortex, the woman died. No changes were found in the adrenal glands, but to my amazement and that of my associates there were typical contracted kidneys. For a long time I was unable to explain this. It was only after improving my knowledge of shock that I found the solution. This woman had contracted kidneys and became uremic, and as a result of this she began to vomit severely. This caused shock, as was shown by the pulse and blood pressure. Although the skin of chronically nephritic persons is occasionally pigmented, the remarkable pigmentation in this case, added to the other symptoms, had led me astray.

A woman aged 45 had been ill for five weeks. She had high fever and disturbed micturition. The urine contained much pus. I was called because her heart action was bad. I found her in typical shock, lying flat in bed, with a rapid pulse (almost impalpable) and a blood pressure of 80 mm. systolic. The nose was cold. There was marked cyanosis. There was no enlargement of the heart. A roentgenogram taken from a distance of 1 meter with the patient supine showed a small heart, the maximal diameter being 9.5 cm. There were no pigmentations. I made a diagnosis of shock, the cause of which I did not know. I thought of infectious shock because of the severe pyelitis. It was peculiar and characteristic of the ever similar picture of shock that a head nurse remarked: "If I didn't know better, I should say she is in diabetic coma." The erythrocyte count was 8,060,000 per cubic millimeter. The alkali reserve was 30 volumes per cent, the blood urea 3 Gm. per liter. By infusion of Bayliss' fluid and Ringer's solution and epinephrine I succeeded in overcoming the shock; the blood pressure rose to 120 systolic and 80 diastolic, the pulse became more easily palpable and slower, and the erythrocyte count fell to 4,700,000 per cubic millimeter. Meanwhile, tubercle bacilli were found in the urine. It was only then that the possibility of Addison's disease was considered. The sodium content of the blood was 285 mg. per hundred cubic centimeters. An extract of adrenal cortex was administered. The patient died, and besides unilateral renal tuberculosis there was observed bilateral caseating tuberculosis of the adrenal glands.

A patient was admitted in a dehydrated condition, with a very low blood pressure and a rapid pulse. At home she had vomited a great deal. She was slightly uremic; the blood was concentrated. In view of the marked emaciation I first thought of cancer of the stomach. With the former cases in mind, however, I thought also of Addison's disease. A very low level of blood sodium sustained this presumption, and treatment with an extract of adrenal cortex brought immediate relief. After this extract was withdrawn the condition became worse. On a diet with much salt and little potassium the woman did well. A close examination did not reveal carcinoma.

These cases show that shock for which no certain cause can be demonstrated should always suggest Addison's disease even in the absence of pigmentation, which absence, in my experience, is anything but rare.

*Acute Pancreatitis.*—Shock is a common symptom of acute pancreatitis. I saw a woman who had high fever shortly after obstetric delivery, with abdominal pain, which, however, was not prominent. She was in severe shock. No cause was known. During the preparation for an infusion she died. At autopsy extensive pancreatitis with fat necrosis was observed. In cases of pancreatitis high red cell values, up to 9,000,000, are often found. The cause of shock in this case is not known; that histamine-like substances were liberated from the necrotic tissues is suggested as a possibility.

*Acute Peritonitis.*—The facies hippocratica so often described in cases of acute peritonitis is an expression of shock. In these cases a reduced circulating blood volume is always found. This shock is clearly understood when one keeps in mind the stagnation of blood in the capillaries over so great a surface as the peritoneum. Besides, there is exudate, which means an escape of plasma through the walls of the blood vessels.

*Combustion and Congelation.*—In these conditions the reduction of the blood volume is the result of extravasation of plasma. Excessive rise of hemoglobin is found, with a normal level of plasma protein. Underhill once found 230 per cent of hemoglobin. In congelation the findings are materially the same. In the treatment of these conditions the management of shock deserves more consideration than has generally been given it.

*Anaphylaxis.*—I observed a considerable rise of the red cell count during extensive serum disease in 2 cases.

A patient with ulcerative colitis was treated with large quantities of dysentery serum. After receiving the last injection of 80 cc. she had an extensive serum rash, occupying practically the whole cutaneous surface. The pulse was impalpable, and the blood pressure could not be measured. The clinical impression was that of shock. The red cell count, determined a few days before at 4,500,000, rose in a few hours to 6,000,000. It was remarkable how I failed to determine the circulating blood volume. When congo red was injected, it immediately disappeared from the blood and was stored in the urticarial wheals, which became fiery red. One can hardly imagine a better demonstration of the permeability of the vessels. For this patient an intravenous drip infusion was established. The blood pressure kept falling over and over again until the third day, when it was maintained on a constant level, perhaps by the simultaneous administration of 50 cc. of an extract of adrenal cortex. Until then the fluid had run away through the vessel walls in spite of the addition of epinephrine, as was seen from the grave edema that had developed.

A patient with ulcerative colitis was given a blood transfusion from a donor of the same blood group, the samples mixing without agglutination. Fifteen

minutes after the transfusion generalized urticaria developed. The blood pressure was 50 mm. systolic, and the pulse was rapid. There was a clinical picture of shock, though not severe. The erythrocyte count previously had been 3,900,000 per cubic millimeter. During the shock it was 7,000,000. The protein content of the plasma was 6.34 per cent. A few hours later, after the shock had passed, these values were respectively 4,900,000 and 6.12 per cent; hence there had occurred exudation of plasma. The patient, a woman, was treated only with 50 cc. of extract of adrenal cortex; the shock was over in two hours, whether or not as a result of this treatment, I do not know.

### TREATMENT

In briefly summarizing the treatment, I may state that cardiotonics do not accomplish anything, which means that they should be left alone. Certain attempts may, however, be made to combat shock. One may try to stimulate the vasomotor system, for instance, with carbon dioxide. The administration of carbon dioxide should always be combined with that of oxygen, as acapnia by itself might cause shock. Loss of heat must be avoided; the blood volume is augmented by warmth. As medicines, one may give strychnine, metrazol, caffeine or camphor. I have never had an impression that they helped. As peripheral vascular stimulants, one may try epinephrine, paramethylaminoethanolphenol tartrate (sympatol), ephedrine and solution of posterior pituitary. These drugs, in my experience, are helpful principally if introduced directly into the blood together with much fluid. As shock is based on reduced blood volume, there can be only one causal treatment: replenishment of the deficient blood volume. In treating for shock from hemorrhage I have used blood; in treating for shock from other causes, Ringer's solution, or saline solution if the chloride value is low. Bayliss' fluid may be tried if the viscosity of the blood is not increased. Acidosis is combated with alkalis. Attempts may be made to improve the relation of fluid in the vascular system, e. g., with substances that act on the peripheral blood vessels or with substances that lessen the permeability of the vessels (perhaps an extract of adrenal cortex).

# INCIDENCE OF FATAL CARDIOVASCULAR DISEASE IN CHARLESTON, S. C.

## WITH PARTICULAR REFERENCE TO HYPERTENSION

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A series of 2,066 consecutive autopsies performed by the staff of the department of pathology of the Medical College of the State of South Carolina from Jan. 1, 1928 through May 1938 has been reviewed by us as a statistical study of cardiovascular disease in the South, particularly among American Negroes. Instances of trauma to the heart or vessels have been excluded, but all other cases are included.

During this period all the autopsies done in the County of Charleston were performed by a member of this staff, including investigations authorized by the coroner in cases of sudden death. Furthermore, since most of the cases prior to about 1935 were from the charity services of the Roper Hospital—a general county hospital for white persons and Negroes—there has been little or no migration of patients, and the results as given here can be taken as representative of fatal cardiovascular disease in this area, at least in the Negro. During this period of ten years the autopsy rate in this hospital has risen from about 25 to about 50 per cent. Since about 1935 the autopsy rate for the white and that for the Negro group have been about equal, while prior to that time the autopsy rate for the white patients, especially those not dependent on charity for hospitalization, was low. Hence the figures for the white race prior to 1935 may not be truly representative.

In 518 of the 2,066 cases (25.07 per cent of the total number of autopsies) death was thought to be a direct or indirect result of cardiovascular disease, while in 106 other cases the changes relative to the cardiovascular system were thought to be more or less incidental, and not themselves the cause of death. The corresponding clinical records

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were also studied, and pertinent data were recorded. The cases were then classified on an etiologic basis.

### CRITERIA FOR CLASSIFICATION

The term congenital heart disease, as used here, does not include patent ductus arteriosus or patent foramen ovale in infants. Four cases of perforate interventricular septum (in 2 of which there were other congenital cardiac anomalies) and 1 case of transposition of the aorta and the pulmonary artery were encountered. Numerous other relatively minor congenital defects were observed, none of which was thought to be the cause of death.

The accurate definition of criteria for the diagnosis of hypertensive cardiovascular disease was difficult. It is known that the blood pressure may be temporarily raised to hypertensive levels without actual cardiovascular disease being present. Furthermore, some patients admitted with congestive heart failure or in some other terminal state may not show clinical hypertension, although the patient is known to have had high blood pressure previously and shows evidence of hypertensive cardiovascular disease at autopsy. Hence the level of blood pressure as the sole determining factor is not always a satisfactory criterion. Some patients show no appreciable hypertrophy of the heart at autopsy, although clinical hypertension has been present for several years. Finally, some persons show hypertension clinically and hypertrophy of the heart, but the kidneys reveal little gross or microscopic change. No single factor seems adequate for the classification of cases in this group. We have adopted three criteria for the postmortem classification of cases of hypertensive cardiovascular disease, viz:

1. Clinical evidence of hypertension during life (diastolic pressure of 100 mm. or above, or systolic pressure of 160 mm. or above provided the diastolic pressure is not below 70 mm.).

2. Cardiac hypertrophy without valvular faults (weight of heart above 500 Gm.).

3. Contracted kidneys (weight 125 Gm. or less), with microscopic evidence of arteriolosclerosis.

With few exceptions, in the cases classified here as those of hypertension at least two of these features have been shown. About 5 cases have been included in which the conditions met only one of these rigid requirements, but came close to the other two. These fitted into no other classification and appeared to belong in this group. Cases in which the criteria just listed were met but the patients died of some condition other than cardiovascular disease are not included in the tables under this heading. Unless there was evidence of congestive heart

failure, of uremia or of vascular accident the hypertension was regarded as incidental.

In the third group, that of cases of arteriosclerotic disease, are included instances in which there was no evidence of hypertensive disease as already listed and death was the result of advanced arterial lesions. Cases in which there were pronounced arterial changes, without evidence of hypertension at the time of death, and the patient died of coronary occlusion, cerebral hemorrhage, mesenteric thrombosis or the like are included in this group.

In the group of cases of syphilitic cardiovascular disease there were patients dying of syphilitic aortic valvulitis with congestive heart failure, from occlusion of the ostiums of the coronary arteries by syphilitic scars and plaques in the aorta, from syphilitic aneurysm (causing death by rupture and hemorrhage or by compression of vital structures) and from syphilitic myocarditis. The last diagnosis is open to criticism, since in only 1 instance, a case of congenital syphilis, were spirochetes demonstrated in the myocardium. The patients whose condition was so diagnosed had strongly positive Kolmer and Kahn reactions ante mortem and showed inflammatory lesions in the myocardium of a chronic nature.

The group of patients with rheumatic heart disease includes those dying of active rheumatic carditis and those dying as a result of residual scars in the valves and myocardium of rheumatic origin which resulted in congestive heart failure.

In the group of cases of "inflammatory" heart disease are included those of acute and subacute bacterial endocarditis, a few cases of severe acute myocarditis, cases of tuberculous pericarditis, in which death apparently resulted from cardiac embarrassment rather than from tuberculous infection and cases of fatal acute pericarditis without other evidence of vascular disease. Cases of syphilitic cardiovascular disease and of rheumatic carditis are not included here. Cases of adherent pericardium of unknown cause are listed under this heading, but when the pericarditis could be shown to be tuberculous in origin it was so classified.

The group of cases of chronic pulmonary disease with heart failure includes cases of pulmonary fibrosis from the inhalation of irritant dusts (particularly asbestos in this locality) and cases of emphysema following asthma and other conditions in persons dying of congestive heart failure for which no other cause could be found.

The grouping of cases of vitamin $B_1$ deficiency under cardiovascular disease is open to question, but each of the children whose condition was so diagnosed apparently died of vascular failure, showed a large heart and had a more or less definite history of vitamin deficiency.

TABLE 1.—*Relative Incidences of the Various Etiologic Types of Cardiovascular Disease According to Race and Sex Observed at 518 Consecutive Autopsies in Cases of Fatal Cardiovascular Disease*

| | Males | | | | Females | | | | All White Patients | | All Negro Patients | | All Males | | All Females | | All Patients | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | White | | Negro | | White | | Negro | | | | | | | | | | | |
| Type | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Congenital heart disease | 1 | 2.1 | 2 | 0.7 | 0 | 0 | 2 | 1.3 | 1 | 1.5 | 4 | 0.9 | 3 | 0.9 | 2 | 1.2 | 5 | 1.0 |
| Hypertensive vascular disease | 16 | 34.0 | 186 | 62.6 | 7 | 33.3 | 80 | 52.3 | 23 | 33.8 | 266 | 59.1 | 202 | 58.7 | 87 | 50.0 | 289 | 55.8 |
| Arteriosclerotic disease | 16 | 34.0 | 14 | 4.7 | 6 | 28.5 | 18 | 11.8 | 22 | 32.4 | 32 | 7.1 | 30 | 8.7 | 24 | 13.8 | 54 | 10.4 |
| Syphilitic vascular disease | 3 | 6.4 | 51 | 17.2 | 0 | 0 | 13 | 8.5 | 3 | 4.4 | 64 | 14.2 | 54 | 15.7 | 13 | 7.5 | 67 | 12.9 |
| Rheumatic heart disease | 3 | 6.4 | 7 | 2.4 | 2 | 9.5 | 10 | 6.5 | 5 | 7.4 | 17 | 3.8 | 10 | 2.9 | 12 | 6.9 | 22 | 4.3 |
| "Inflammatory" heart disease | 8 | 17.0 | 29 | 9.8 | 5 | 23.8 | 28 | 18.3 | 13 | 19.1 | 57 | 12.7 | 37 | 10.8 | 33 | 19.0 | 70 | 13.5 |
| Heart failure due to pulmonary disease | 0 | 0 | 6 | 2.0 | 1 | 4.8 | 1 | 0.7 | 1 | 1.5 | 7 | 1.6 | 6 | 1.7 | 2 | 1.2 | 8 | 1.5 |
| Beriberi heart | 0 | 0 | 2 | 0.7 | 0 | 0 | 1 | 0.7 | 0 | 0 | 3 | 0.7 | 2 | 0.6 | 1 | 0.6 | 3 | 0.6 |
| Total number | 47 | 99.9 | 297 | 100.1 | 21 | 99.9 | 153 | 100.1 | 68 | 100.1 | 450 | 100.1 | 344 | 100.0 | 174 | 100.2 | 518 | 100.0 |

ETIOLOGIC CLASSIFICATION OF CASES

The cases of fatal cardiovascular disease are classified in table 1 as to etiologic type, race and sex.

Perusal of this table reveals several noteworthy facts. The incidence of hypertensive cardiovascular disease is exceedingly high, especially in the Negro, being almost twice as common, sex for sex, as in the white race. Among Negro males it comprises 62.6 per cent of all cases of cardiovascular disease, and the incidence is only slightly lower (52.3 per cent) for Negro females. Among white males hypertensive cardiovascular disease accounts for 34 per cent of the cardiovascular deaths, and among white females, for 33.3 per cent. In white males arteriosclerosis (without hypertension) is as commonly a cause of death as is hypertension, but in Negro males arteriosclerosis accounts for a relatively small proportion of deaths. As would be expected from the relatively

TABLE 2.—*Sexual Differences in Incidence of Etiologic Types of Cardiovascular Disease*

| Etiologic Type | Males, Percentage | Females, Percentage |
|---|---|---|
| 1. Congenital heart disease | 60.0 | 40.0 |
| 2. Hypertensive cardiovascular disease | 69.9 | 30.1 |
| 3. Arteriosclerotic disease | 40.7 | 59.3 |
| 4. Syphilitic cardiovascular disease | 80.6 | 19.4 |
| 5. Rheumatic heart disease | 45.5 | 54.5 |
| 6. "Inflammatory" heart disease | 52.9 | 47.1 |
| 7. Heart failure due to pulmonary disease | 75.0 | 25.0 |
| 8. Beriberi heart | 66.7 | 33.3 |
| All types | 66.4 | 33.6 |

high rate of syphilis among Negroes, syphilitic cardiovascular disease is an important cause of death in that race, while in the white race it is much less common.

In table 2 the total number of cases in each etiologic group is distributed between the sexes. The number of cases in groups, 1, 5, 7 and 8 is too small for the figures to be significant. In the other classifications the figures are probably reasonably representative. Hypertensive cardiovascular disease is more than twice as common in the male as in the female, and syphilitic cardiovascular disease is four times as common in the male. Arteriosclerotic disease is slightly more frequent in the female than in the male. All types of cardiovascular disease combined are twice as common in the male as in the female.

The large group of patients with hypertension (white, 23; Negro, 266) is divided further in table 3 as to the actual manner of death. The average age at death for each group is also included. (In the Negro race the age given by the patient is frequently unreliable. It is not uncommon for a gray-haired, edentulous Negro man to give his age as 22. This was corrected in so far as possible by comparing the

stated age with the estimated age at death. If the two agreed within a decade, the stated age was taken to be correct, since the limits of error of the estimation are rather wide. If the estimated age exceeded the stated age by more than a decade, the former was taken to be correct.)

In many cases of hypertensive cardiovascular disease autopsy revealed more than one of the factors previously listed. Cases of combined factors are listed under the heading of the condition which seemed to have caused the death (i. e., rupture or dissection of the aorta took precedence over all other classifications; cerebral hemorrhage came next; then coronary thrombosis).

TABLE 3.—*Manner of Death in 289 Cases of Fatal Hypertensive Cardiovascular Disease, with Age at Death*

| Cause of Death | White Patients | | | Negro Patients | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Percentage | Average Age | No. | Percentage | Average Age | No. | Percentage | Average Age |
| Uncomplicated, with heart failure | 8 | 34.8 | 61 | 97 | 36.5 | 51 | 105 | 36.3 | 52 |
| Azotemia * | 7 | 30.4 | 46 | 64 | 24.1 | 44 | 71 | 24.6 | 44 |
| Uremia * and edema | 2 | 8.7 | 43 | 22 | 8.3 | 41 | 24 | 8.3 | 41 |
| Coronary thrombosis | 1 | 4.4 | 48 | 9 | 3.4 | 45 | 10 | 3.5 | 45 |
| Cerebral hemorrhage or thrombosis | 4 | 17.4 | 65 | 57 | 21.4 | 49 | 61 | 21.1 | 50 |
| Thrombotic gangrene (of extremity, etc.) | 1 | 4.4 | 55 | 5 | 1.9 | 51 | 6 | 2.1 | 51 |
| Hypertension plus aortic insufficiency (usually syphilitic) with heart failure | 0 | 0 | .. | 9 | 3.4 | 41 | 9 | 3.1 | 41 |
| Rupture or dissection of aorta | 0 | 0 | .. | 3 | 1.1 | 43 | 3 | 1.0 | 43 |
| | 23 | 100.1 | 55 | 266 | 100.1 | 47 | 289 | 100.0 | 48 |

* Azotemia or uremia, as employed here, signifies an elevation of the urea nitrogen in the blood to 50 mg. per hundred cubic centimeters or above, or of the creatinine to 5 mg. per hundred cubic centimeters or above, together with other evidences of uremia (clinical and at autopsy).

It is worthy of note in this table that while the incidence of hypertensive cardiovascular disease is much greater in the Negro than in the white group, the manner of death for the two groups is about the same. The high incidence of uremia as a manner of death is shown. In each group it can be noted that the Negro died at an earlier age than did the white man. It is especially noteworthy that the Negro died of apoplexy, associated with hypertension, sixteen years earlier than the white man.

That aortic insufficiency and hypertension may occur together in the same case has received scant notice in the literature. In such cases the diastolic pressure may fall below the level generally taken to indicate hypertension, but the systolic pressure tends to remain high. The average of the highest systolic blood pressures recorded in these cases was 205 mm.; that of the highest diastolic blood pressures, 100 mm. In almost all these cases the condition was diagnosed clinically as aortic

insufficiency due to syphilis, although in some it was diagnosed as hypertensive cardiovascular disease when the murmurs in the aortic area were not characteristic. In 7 of the 9 cases in which aortic insufficiency was associated with hypertension, the insufficiency was due to syphilitic scarring of the aortic valves and commissures. In the other 2 cases it appeared that there had been an incomplete transverse rupture of the aorta just above the commissures of the aortic valve, similar to the intimal rupture that occurs in dissecting aneurysm; the active process of rupture had healed, leaving a slitlike gap in the aortic wall, covered by endothelium, which permitted the aortic cusps to fall back into the ventricle during diastole. In both these cases there were the typical aortic diastolic murmur of aortic insufficiency and the wide pulse pressure that goes with that condition. One of these patients, several months before his admission to the hospital, had suffered severe sub-

TABLE 4.—*Manner of Death in 54 Cases of Fatal Arteriosclerotic Disease (Without Evidence of Hypertension), with Age at Death*

| Cause of Death | White Patients | | | Negro Patients | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age |
| Generalized arteriosclerosis (without hypertension) as a cause of death | 9 | 40.9 | 73 | 12 | 37.5 | 67 | 21 | 38.9 | 70 |
| Coronary thrombosis without hypertension | 8 | 36.4 | 59 | 4 | 12.5 | 65 | 12 | 22.2 | 61 |
| Other vascular accident without hypertension | 5 | 22.7 | 59 | 16 | 50.0 | 56 | 21 | 38.9 | 57 |
| | 22 | 100.0 | 65 | 32 | 100.0 | 61 | 54 | 100.0 | 63 |

sternal pain. This had subsequently disappeared, although the cardiac failure, as manifested by edema, did not occur until a day or so after the pain. This pain may well have been the time at which the short dissection (if we may call it that) occurred.

It is interesting to note that the incidence of syphilitc aortic insufficiency for the total group of hypertensive patients was 2.06 per cent; for the whole autopsy group it was 2.23 per cent.

The group of 54 cases of fatal arteriosclerotic disease (22 white persons, 32 Negroes) is subdivided in table 4 according to the manner of death. It can be seen that coronary thrombosis without hypertension is relatively rare in the Negro, but that other vascular accidents are extremly common. In the whole series of cases of fatal cardiovascular diseases, hypertensive and nonhypertensive, there were 13 cases (2.9 per cent) of coronary thrombosis in the Negro and 9 cases (13.2 per cent.) in the white. In two thirds of the cases of coronary thrombosis among Negroes the condition was associated with evidence of hypertension, but in only one ninth of those in the white group was the dis-

ease thought to be associated with hypertension. Likewise, in the whole group of cases of fatal cardiovascular disease death was from vascular accident other than coronary in 10 cases (14.7 per cent) of the white group and in 81 cases (18 per cent) of the Negro group. (Cerebral hemorrhages due to tumor of the brain, congenital aneurysms and the like are not included.) In the white group half of the vascular accidents other than coronary occurred without evidence of hypertension at the time of death, but in the Negroes more than 80 per cent of the vascular accidents other than coronary occurred with evidence of hypertension. Most of the cases of "vascular accident" listed here were instances of cerebral hemorrhage or thrombosis. This accident seems to occur in the Negro more than ten years earlier than in the white person.

Syphilitic cardiovascular disease was the cause of death in 67 patients; 64 of these were Negroes and 3 white persons. The cases are

TABLE 5.—*Manner of Death in 67 Cases of Fatal Syphilitic Cardiovascular Disease, with Age at Death*

| Cause of Death | White Patients | | | Negro Patients | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age |
| Syphilitic aortic insufficiency with heart failure | 0 | 0 | .. | 29 | 45.3 | 39 | 29 | 43.3 | 39 |
| Narrowing of coronary ostiums by syphilitic plaques in the aorta | 2 | 66.7 | 42 | 9 | 14.1 | 45 | 11 | 16.4 | 44 |
| Fatal syphilitic aneurysm of any vessel | 1 | 33.3 | 45 | 21 | 32.8 | 43 | 22 | 32.8 | 43 |
| Syphilitic myocarditis | 0 | 0 | .. | 5 | 7.8 | 28 | 5 | 7.5 | 28 |
| | 3 | 100.0 | 43 | 64 | 100.0 | 40 | 67 | 100.0 | 40 |

subdivided in table 5 according to the manner of death. (Frequently two or more of these conditions were combined in a single case. If so, the case has been listed under the condition thought most likely to be the cause of death; thus, a ruptured aneurysm took first preference, syphilitic narrowing of the coronary ostiums second and syphilitic aortic insufficiency third.)

It is obvious that the number of cases of syphilitic cardiovascular disease in the white race is too small for any interpretation to be placed on their distribution among groups. In the Negroes syphilitic aortic valvulitis, with insufficiency and congestive heart failure, was the commonest cause of death, although aneurysm was frequently an important factor. In the few cases of syphilitic narrowing of the coronary ostiums which were encountered, death was usually sudden, occurring particularly during exertion or emotional strain, and unless the lesion was associated with insufficiency of the aortic valve, there was usually no evidence of edema. A great many cases of uncomplicated syphilitic aortitis were encountered in this series, but in none was it the cause

of death. Wilson [1] studied the cases of syphilitic aortitis in this service during the period covered by this study and has reported on them.

Rheumatic heart disease was the cause of death in 22 cases; 5 of the patients were white and 17 Negroes, with the distribution shown in table 6. Rheumatic heart disease is relatively rare in Charleston, although the incidence varies somewhat from year to year. The number of cases is about evenly divived between patients dying during

TABLE 6.—*Manner of Death in 22 Cases of Fatal Rheumatic Cardiovascular Disease, with Age at Death*

| Cause of Death | White Patients | | | Negro Patients | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age |
| Active rheumatic carditis | 2 | 40 | 11 | 9 | 52.9 | 20 | 11 | 50 | 18 |
| Rheumatic sequelae with heart failure | 3 | 60 | 54 | 8 | 47.0 | 26 | 11 | 50 | 34 |
| | 5 | 100 | 37 | 17 | 99.9 | 23 | 22 | 100 | 26 |

TABLE 7.—*Manner of Death in 70 Cases of Fatal "Inflammatory" Cardiovascular Disease (Nonrheumatic, Nontuberculous), with Age at Death*

| Cause of Death | White Patients | | | Negro Patients | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age | No. | Per-centage | Aver-age Age |
| Acute bacterial endocarditis | 6 | 46.2 | 48 | 11 | 19.3 | 43 | 17 | 24.3 | 45 |
| Subacute bacterial endocarditis | 2 | 15.4 | 20 | 2 | 3.5 | 35 | 4 | 5.7 | 27 |
| Acute myocarditis | 1 | 7.7 | 75 | 9 | 15.8 | 53 | 10 | 14.3 | 57 |
| Tuberculous pericarditis | 0 | 0 | .. | 18 | 31.6 | 37 | 18 | 25.7 | 37 |
| Acute pericarditis (nonrheumatic, nontuberculous) | 3 | 23.1 | 36 | 13 | 22.8 | 26 | 16 | 22.9 | 28 |
| Adhesive pericarditis | 1 | 7.7 | 65 | 3 | 5.3 | 45 | 4 | 5.7 | 50 |
| Chronic myocarditis* | 0 | 0 | .. | 1 | 1.8 | 35 | 1 | 1.4 | 35 |
| | 13 | 100.1 | 44 | 57 | 100.1 | 35 | 70 | 100.0 | 37 |

*A case of chronic inflammatory disease of the myocardium of unknown origin, apparently not syphilitic.

the active stage of inflammation of the heart and those dying as a result of residual effects (usually mitral stenosis). Although our total number of cases is small, and therefore may not be representative, the process seems to affect the white race relatively more than the Negro.

The group of "inflammatory" heart disease (nonrheumatic and nonsyphilitic) comprised 70 cases, 13 of white persons and 57 of Negroes. They are classified in table 7.

1. Wilson, R., Jr.: Studies in Syphilitic Cardiovascular Disease: I. Uncomplicated Syphilitic Aortitis, an Asymptomatic Condition, Am. J. M. Sc. **194**:178, 1937.

It can be seen that tuberculosis of the pericardium was not the cause of a single death from heart failure in the white group, but was a relatively common cause of death in the Negro group. This corresponds with the much higher incidence of tuberculous infection in the Negro than in the white population in this region. Even when allowance is made for the difference in the total number of cases in the two races due to the high incidence of tuberculous pericarditis, it seems that acute and subacute bacterial endocarditis are more common in the white than in the Negro race. No obvious explanation for this is apparent; it may reflect merely the greater interest of the resident staff in securing autopsies on that group of the white patients, while in the cases of cardiovascular disease that seemed to be of less interest clinically per-

TABLE 8.—*Relative Incidence of the Various Types of Cardiovascular Disease Causing Death by Heart Failure*

| Cause of Death | White Patients | | Negro Patients | | All Patients | |
|---|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | No. | Percentage |
| Congenital heart disease | 1 | 3.7 | 4 | 1.8 | 5 | 2.0 |
| Hypertensive cardiovascular disease | 9 | 33.3 | 119 | 53.1 | 128 | 51.0 |
| Hypertensive disease plus valvular disease | 1 | 3.7 | 10 | 4.5 | 11 | 4.4 |
| Hypertensive disease plus coronary thrombosis | 1 | 3.7 | 9 | 4.0 | 10 | 4.0 |
| Coronary thrombosis, without hypertension | 8 | 29.6 | 4 | 1.8 | 12 | 4.8 |
| Syphilitic aortic insufficiency | 0 | 0 | 29 | 12.9 | 29 | 11.6 |
| Syphilitic narrowing of coronary ostiums | 2 | 7.4 | 9 | 4.0 | 11 | 4.4 |
| Syphilitic myocarditis | 0 | 0 | 5 | 2.2 | 5 | 2.0 |
| Rheumatic heart disease (residual effects) | 3 | 11.1 | 7 | 3.1 | 10 | 4.0 |
| Tuberculous pericarditis | 0 | 0 | 18 | 8.0 | 18 | 7.2 |
| Adhesive pericarditis | 1 | 3.7 | 3 | 1.3 | 4 | 1.6 |
| Chronic pulmonary disease with heart failure | 1 | 3.7 | 7 | 3.1 | 8 | 3.2 |
| Total no. | 27 | 99.9 | 224 | 99.8 | 251 | 100.2 |

mission for autopsy was not urged. The higher percentage of autopsies among the Negroes than among the white patients in the earlier part of the period covered by this study has already been alluded to.

In table 8 we have listed all cases of death from heart failure, without acute infectious disease, under the headings of the various etiologic factors. The great importance of hypertension as a cause of congestive failure in this locality is shown, especially in the Negro. In the white race coronary thrombosis (when the cases of hypertensive and those of nonhypertensive coronary thrombosis are combined) equals hypertensive cardiovascular disease in importance; in the Negro coronary thrombosis is relatively uncommon. Syphilitic cardiovascular disease causes heart failure more than twice as often in the Negro as in the white race. No case of syphilitic aortic valvulitis with insufficiency was encountered in the series of autopsies on white patients. Rheumatic heart disease seems to be more frequently a cause of congestive failure

in the white than in the Negro group, but the number of cases is too small for the conclusion to be definite.

Table 8 can be compared with tables prepared by authors in other localities, in which the relative incidence of the various types of heart disease is given. Such comparison must be made with great caution, however, since many factors are involved. Most of the studies available for comparison are clinical, and relatively few autopsy data can be found in the literature. The economic status of the patient, the nature of the cardiac service from which the results were reported and racial factors are only some of the many factors that must be considered in making comparisons. In comparing autopsy statistics on the subject, the autopsy rate in the hospitals concerned and the criteria for diagnosis are important. It is especially important to know whether cases of sudden death are included, as in the cases commonly examined by a medical examiner or coroner.

Suffice it to say at this point that the incidence of hypertensive cardiovascular disease has been shown to be high, especially in the Negro, in studies from Texas,[2] Georgia,[3] Tennessee,[4] the District of Columbia [5] and San Francisco.[6] In New England,[7] New York city [8] and the Rocky Mountain region [9] rheumatic heart disease is of relatively more importance than is hypertensive disease. Whether this means that hypertensive cardiovascular disease in these areas is actually less frequent in the population than it is in the Southern areas, or whether the high incidence of rheumatic heart disease (which is known to be regional in

2. Stone, C. T., and Vanzant, F. R.: Heart Disease as Seen in a Southern Clinic: A Clinical and Pathological Survey, J. A. M. A. **89**:1473 (Oct. 29) 1927. Schwab, E. H., and Schulze, V. E.: The Incidence of Heart Disease and of the Etiological Types in a Southern Dispensary, Am. Heart J. **7**:223, 1931.

3. Davison, H. M., and Thoroughman, J. C.: A Study of Heart Disease in the Negro Race, South. M. J. **21**:464, 1928.

4. Laws, C. L.: The Etiology of Heart Disease in Whites and Negroes in Tennessee, Am. Heart J. **8**:608, 1933.

5. Gager, L. T., and Dunn, W. L.: Heart Disease in Washington, D. C.: A Study of Etiologic Types and the Factors of Race, Age and Sex in One Thousand and Two Hundred Cases, M. Ann. District of Columbia **2**:112, 1933. Hedley, O. F.: A Study of Four Hundred and Fifty Fatal Cases of Heart Disease Occurring in Washington (D. C.) Hospitals During 1932, with Special Reference to Etiology, Race and Sex, Pub. Health Rep. **50**:1127, 1935.

6. Geiger, J. C.; Sampson, J. J.; Miller, R. C., and Gray, J. P.: A Survey of Heart Disease Morbidity in San Francisco, Am. Heart J. **12**:137, 1936.

7. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, Am. Heart J. **3**:302, 1928.

8. Wyckoff, J., and Lingg, C.: Statistical Studies Bearing on Problems of Classification of Heart Disease: II. Etiology in Organic Heart Disease, Am. Heart J. **1**:446, 1926.

9. Viko, L. E.: Heart Disease in the Rocky Mountain Region, Am. Heart J. **6**:264, 1930.

its distribution in the United States) so swells the total of all types of vascular disease that hypertension is given a less important place in statistical studies based on relative, not actual, incidence is a question which must await further studies. Figures available from the registration area of the United States are of little value in solving the question, since they are based on anatomic rather than etiologic diagnoses. The need for revision of the classification of cardiac diseases in the "Manual of the International List of Causes of Death" [10] has been pointed out by Hedley.[11]

### ETIOLOGIC FACTORS IN THE SERIES OF CASES OF HYPERTENSION

An effort was made to ascertain the cause of the hypertension in each of the 289 cases of hypertensive cardiovascular disease. Little satisfaction was derived from this study because of the variation in the

TABLE 9.—*Relative Incidence of Etiologic (?) Factors in Cases of Hypertensive Cardiovascular Disease*

| Etiologic Factor | White Patients | | Negro Patients | | All Patients | |
|---|---|---|---|---|---|---|
| | No. | Percentage | No. | Percentage | No. | Percentage |
| Arteriolar nephrosclerosis | 18 | 78.2 | 229 | 86.1 | 247 | 85.5 |
| Acute glomerulonephritis | 0 | 0 | 3 | 1.1 | 3 | 1.0 |
| Subacute glomerulonephritis | 2 | 8.7 | 1 | 0.4 | 3 | 1.0 |
| Chronic glomerulonephritis | 0 | 0 | 20 | 7.5 | 20 | 6.9 |
| Pyelonephritis | 2 | 8.7 | 7 | 2.6 | 9 | 3.1 |
| Congenital abnormalities | 0 | 0 | 2 | 0.8 | 2 | 0.7 |
| Thyrotoxicosis | 0 | 0 | 1 | 0.4 | 1 | 0.3 |
| Pituitary tumor | 1 | 4.3 | 1 | 0.4 | 2 | 0.7 |
| Eclampsia | 0 | 0 | 2 | 0.8 | 2 | 0.7 |
| Total no. | 23 | 99.9 | 266 | 100.1 | 289 | 99.9 |

terminology used by different pathologists during the ten year period. In the earlier part of the period covered by this report, many of the cases of hypertensive cardiovascular disease were listed, after histologic study of the kidneys, as instances of "chronic glomerular nephritis," while in more recent years in most of the cases the condition has been diagnosed as "nephrosclerosis" or "arteriolar sclerosis of the kidneys." Some of the older slides were reviewed in an attempt to reclassify the group, but in many cases it was impossible to decide between chronic glomerular nephritis and arteriolosclerosis of the kidneys. One can hardly avoid the conclusion that any attempt to differentiate between the two, at least in the later stages, is pointless, either from a clinical or from a pathologic point of view. This is especially true if one admits the incompleteness of knowledge of the early phases of arteriolosclerosis in the kidney and lack of knowledge of its cause. Table 9, indicating

10. Manual of the International List of Causes of Death, ed. 4, United States Department of Commerce, Bureau of the Census, 1929.

11. Hedley, O. F.: Studies of Heart Disease Mortality, Public Health Bulletin 231, United States Treasury Department, Public Health Service, 1936.

the relative incidence of the factors thought to be etiologic, in the light of present day ignorance of the matter, is presented for what it may be worth.

Readers may wonder why many of the aforementioned groups are listed. Since all may be associated with clinical hypertension, with hypertrophy of the heart and with contracted kidneys, and may cause death in the same ways, there seems to be little reason for excluding them. Many cases of acute, subacute and chronic disease of the kidney, of pyelonephritis and of eclampsia in our autopsy records are not included in this study at all, since in these instances the criteria formulated in an earlier part of this paper were not met.

Nine of the 20 patients with chronic glomerulonephritis died of uremia. Their average age was 36 years, which is 8 years younger than the average age for the group with azotemia as a whole.

It is commonly taught that the subacute stage of glomerulonephritis is not associated with hypertension. In the 3 cases listed here the usual criteria for the histologic diagnosis of the subacute phase (most of the glomeruli showing proliferative changes and "epithelial crescents") were met, and at the same time the criteria used here for the diagnosis of hypertensive disease were satisfied.

In only 1 of the 2 cases of pituitary tumor associated with hypertension was the growth of the basophilic type. The other was a chromophobe adenoma. Whether the hypertension in the second case was a result of the tumor or whether the two conditions represented completely independent entities is a question.

### ANNUAL AND SEASONAL VARIATIONS

Since several observers [12] have noted a pronounced difference in the blood pressure averages for large groups of supposedly normal persons, examined under the same circumstances, in different years, the cases of hypertensive disease were divided into groups according to years, and a chart was prepared showing the number of deaths from hypertension in each year as the percentages of all cardiovascular deaths and as the percentages of all autopsies. The results are shown in chart 1.

During the period covered by this study, deaths from hypertensive cardiovascular disease have tended to occur in definite cycles, no matter whether deaths from hypertension are compared with the total number of cardiovascular deaths (curve *1*) or with the total number of autopsies (curve *2*). Furthermore, a division of patients dying of hypertension

12. Alvarez, W. C.; Wulzen, R., and Mahoney, L. J.: Blood Pressures in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July) 1923. Goepp, R. M.: Blood Pressure as a Prognostic Factor, Pennsylvania M. J. **22**: 295, 1919. Symonds, B.: The Blood Pressure of Healthy Men and Women J. A. M. A. **80**:232 (Jan. 27) 1923.

into patients dying of uremia and heart failure combined (curve *3*) and those dying of vascular accident (curve *5*) shows in general the same configuration when expressed as percentages of the total autopsy group. Curve *4*, showing deaths from nonhypertensive cardiovascular diseases expressed as percentages of all autopsies, also indicates variations from year to year.

As a test of the significance of the oscillations in these curves, the low point in 1928 and the peak in 1930 in curve *2* were taken. It was found that the difference in percentages in the two instances was statistically significant, and that chance could bring about the difference between peak and valley in less than 1 per cent of such investigations (as *P* is less than 1 per cent).[13]

A similar investigation of the oscillations in curves *1* and *3* shows that the difference between peak and valley is not beyond the limit of chance, but since the oscillations in curve *2* are statistically significant and since the other curves show in general the same variations and are based on the same cases, it seems reasonable to conclude that deaths from hypertensive cardiovascular disease in Charleston, S. C.,[14] vary greatly from year to year and that the variation is not due to chance. The importance of this observation is apparent. If it could be confirmed by similar studies from other areas, or by an analysis by years of the number of new cases of hypertension seen in various clinics, it might serve as a clue to the factors in a disease which ranks among the chief causes of death in the United States and in the world.

Curve *4*, showing nonhypertensive cardiovascular deaths, was also studied, the valley in 1934 being compared with the peak in 1935. This investigation showed that the difference between the two years is statistically significant. During 1935 the number of deaths from syphilitic cardiovascular disease was particularly increased.

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13. In the formula $S = \frac{n_1\bar{f}_1(1-\bar{f}_1) + n_2\bar{f}_2(1-\bar{f}_2)}{(n_1 + n_2 - 2)} \times \frac{n_2 + n_1}{n_1 n_2}$, S is the standard deviation of the difference between the two percentages, expressed in decimals; $n_1$ is the total number of autopsies (176) performed in 1928; $n_2$ is the total number of autopsies (184) performed in 1930; $\bar{f}_1$ is the percentage of occurrences of deaths from hypertension in 1928, expressed as a decimal (0.102), and $\bar{f}_2$ is the corresponding figure for 1930, expressed as a decimal (0.217). The difference $(\bar{f}_2 - \bar{f}_1)$, or 0.115, is divided by its standard deviation (0.038), and the quotient (3.03) is checked in the table of the distribution of "t."

14. Since there was no unusual concentration by the hospital staff on hypertensive disease during the period covered by these studies, it seems likely that the autopsy figures represent faithfully the trend in the total number of deaths. Furthermore, since the changes in the intern staff in the Roper Hospital are made in July of each year, the difference in the diligence of various intern groups in securing autopsies would be insignificant in statistics based on the calendar year.

Similarly, the total number of deaths from cardiovascular disease in general and from hypertensive cardiovascular disease in particular were subdivided according to the season of the year in which death occurred and were compared with the total number of autopsies performed in that season. Spring was considered as extending from March 1 through May, summer from June 1 through August, fall from September 1 through November and winter from December 1 through

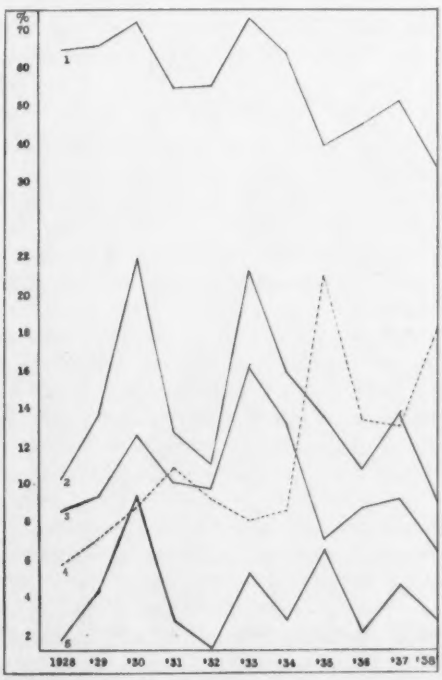


Chart 1.—Annual variations in number of deaths from hypertensive cardiovascular disease.

Curve *1* shows deaths from hypertension, expressed as percentages of all cardiovascular deaths; curve *2*, deaths from hypertension, expressed as percentages of all autopsies; curve *3*, deaths from uremia and heart failure due to hypertension, expressed as percentages of all autopsies; curve *4*, deaths from all nonhypertensive cardiovascular diseases combined, expressed as percentages of all autopsies, and curve *5*, deaths from vascular accidents due to hypertension, expressed as percentages of all autopsies.

February. The total number of autopsies performed in the spring months was 551 and included 69 cases in which death was from hypertensive disease; in the summer months there were 489 autopsies, with

65 cases of death from hypertensive disease; in the fall there were 461 autopsies, with 74 cases of death from hypertensive disease, and in the winter there were 505 autopsies, with 72 cases of death from hypertensive disease. The results of the analysis are illustrated graphically in chart 2. Here, curve *1* shows the number of deaths from hypertension, expressed as percentages of the total number of deaths from all cardiovascular diseases; curve *2* shows deaths from hypertension, expressed as percentages of the total number of autopsies; curve *3*

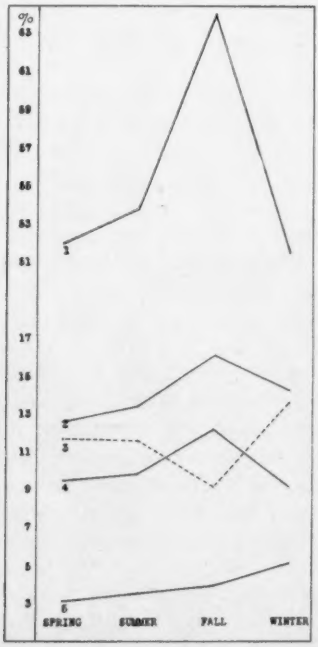


Chart 2.—Seasonal variations in number of deaths from hypertensive cardiovascular disease.

Curve *1*, deaths from hypertension, expressed as percentages of all cardiovascular deaths; curve *2*, deaths from hypertension, expressed as percentages of all autopsies; curve *3*, deaths from all nonhypertensive cardiovascular diseases combined, expressed as percentages of all autopsies; curve *4*, deaths from uremia and heart failure due to hypertension, expressed as percentages of all autopsies, and curve *5*, deaths from vascular accidents due to hypertension, expressed as percentages of all autopsies.

shows deaths from cardiovascular diseases not of hypertensive origin, expressed as percentages of all autopsies; curves *4* and *5* show a division of deaths from hypertension into those from uremia and heart

failure combined (curve *4*) and those from vascular accidents (curve *5*), in each instance expressed as percentages of all autopsies. The curves show a moderate rise in the number of deaths from hypertension in the fall, whereas the deaths from nonhypertensive cardiovascular disease were relatively more numerous in the winter months. Analysis of these figures shows that the variations are not beyond the margin of error. The fact that they are not does not mean that the variations are of no significance. Similar investigations from other sources would be of interest.

At present we are not prepared to draw conclusions from these graphs. An investigation of possibly related factors will be undertaken at an early date.

## SUMMARY

In a series of 2,066 consecutive autopsies performed in Charleston, S. C., all cases in which death was from cardiovascular disease have been studied, using the clinical record, the autopsy protocol and, in many instances, the microscopic slides. These cases were then classified according to etiologic factors. Hypertensive cardiovascular disease was the etiologic factor in more than half the cases. When only cases of congestive heart failure were studied, it was noted that hypertensive cardiovascular disease again more than equaled all other etiologic types of heart disease combined. The incidence of hypertension was particularly high in the Negro race, and especially in the Negro male. While hypertension was common in the white race also, arteriosclerotic disease (without hypertension) was almost as frequently a cause of death. Syphilitic cardiovascular disease was seldom encountered in the white patients in this series.

Each etiologic group of cases of vascular disease was further divided according to the manner of death, and the average age at death was shown. In almost every category the Negro died earlier of vascular disease than did the white patient.

Coronary thrombosis, either with or without hypertension, was seldom encountered in the Negro, but in the white group it was common.

An attempt to classify the cases of hypertensive cardiovascular disease according to the factors bringing about hypertension met with little success.

The annual variations in deaths from hypertensive cardiovascular disease in this locality was studied, and the oscillations in the graph were shown to be greater than would be expected if chance alone were the important factor. This offers a lead for consideration in attempts to learn the cause of hypertensive disease.

Seasonal variations in deaths from hypertensive diseases were also shown, but these variations could be accounted for by chance error.

# BLOOD "GUANIDINE"

## FURTHER OBSERVATIONS

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AND
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In a recent article,[1] one of us (R. H. M.) presented the results of estimations of the "guanidine" content of the blood of 800 patients with arterial hypertension. An increase in blood "guanidine" was found in 32 per cent of hypertensive persons with normal values for nonprotein nitrogen in the blood and in a higher percentage of patients with nitrogen retention. These observations have led directly to the following study, in which we have investigated the association in animals between high values for blood "guanidine" and the blood pressure and have also studied further the properties of the substance in the blood which with certain reagents gives a color like that of guanidine derivatives and which we have referred to as "guanidine."

Estimations of the blood pressure in these experiments were carried out by the palpatory method on carotid loops, a method permitting estimation only of the systolic pressure. Several different experimental procedures were employed; all caused renal insufficiency, some with and some without elevation in the blood pressure. In the first 3 experiments an arteriovenous fistula between the renal artery and the renal vein was formed and the remaining kidney removed at that time or later. This procedure in three instances produced marked elevation in blood pressure with renal insufficiency.

### EXPERIMENTS

EXPERIMENT 1.—A dog weighing 12.1 Kg. was used. The blood pressure from Nov. 9 to Nov. 14, 1938 varied from 80 to 120.

On November 14 an arteriovenous fistula of the left renal artery and vein was created. The following observations were made:

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From the Hixon Laboratory of Medical Research, the University of Kansas School of Medicine.

1. Major, R. H.: Blood "Guanidine" in Arterial Hypertension, Arch. Int. Med. **62**:946-948 (Dec.) 1938.

| Date | Blood Pressure | Nonprotein Nitrogen | Creatinine | "Guanidine" | Comment |
|---|---|---|---|---|---|
| 11/15/38 | 95 | 31 | 1.4 | 0.21 | |
| 11/16/38 | 110 | 25.7 | 1.4 | 0.21 | |
| 11/16/38 to 11/25/38 | 100 to 125 | | | | |
| 11/25/38 | 110 | 41 | 1.5 | 0.22 | |
| 11/26/38 | 175 | 71 | 3.8 | 0.24 | Right kidney removed |
| 11/27/38 | 185 | 127 | 11.3 | 0.58 | |
| 11/28/38 | 130 | 174 | 16.3 | 0.87 | Severe vomiting |
| 11/29/38 | 165 | 193 | 18.1 | 1.04 | |
| 11/30/38 | 165 | 259 | 22.2 | 1.46 | |
| 12/ 1/38 | 165 | 305 | 23.9 | 0.88 | No urine voided since 11/25 |
| 12/ 2/38 | | | | | Animal found dead |

EXPERIMENT 2.—A dog weighing 15.4 Kg. was used. An arteriovenous fistula of the right renal artery and vein was produced on Sept. 22, 1938. The blood pressure from September 22 to November 17 varied from 55 to 130. The following data were obtained:

| Date | Blood Pressure | Nonprotein Nitrogen | Creatinine | "Guanidine" | Comment |
|---|---|---|---|---|---|
| 10/17/38 | 65 | 23 | 1.4 | 0.2 | |
| 10/18/38 | 125 | 48 | 3.5 | 0.39 | Left kidney removed |
| 10/19/38 | 135 | | | | |
| 10/20/38 | 90 | | | | |
| 10/21/38 | 110 | | | | |
| 10/22/38 | 150 | 142 | 16 | 1.13 | |
| 10/24/38 | 170 | 272 | 21.5 | 1.15 | |
| 10/25/38 | 140 | 321 | 27.7 | 1.96 | |
| 10/26/38 | 100 | 300 | 27.6 | 2.03 | |
| 10/27/38 | | | | | Dog found dead |

EXPERIMENT 3.—A dog weighing 14.7 Kg. was used. The following data were obtained:

| Date | Blood Pressure | Nonprotein Nitrogen | Creatinine | "Guanidine" | Comment |
|---|---|---|---|---|---|
| 11/10/38 | 140 | | | | |
| 11/11/38 | 135 | | | | |
| 11/12/38 | 130 | | | | |
| 11/13/38 | 145 | | | | |
| 11/14/38 | 125 | 32 | 1.4 | 0.18 | |

An arteriovenous fistula was made in the left renal artery and vein. The right kidney was removed. The following additional data were obtained:

| Date | Blood Pressure | Nonprotein Nitrogen | Creatinine | "Guanidine" | Comment |
|---|---|---|---|---|---|
| 11/15/38 | 170 | 88 | 5.6 | 0.6 | |
| 11/16/38 | 170 | 157 | 9.6 | 1.4 | |
| 11/17/38 | 190 | 250 | 12.1 | 1.23 | |
| 11/18/38 | | | | | Dog found dead |

In summary, the results of these 3 experiments show that in each instance there was a marked rise in systolic blood pressure accompanied by retention of nitrogen and a great increase in the "guanidine" content of the blood.

In the following experiment one kidney was removed and a Goldblatt clamp placed on the vein of the other kidney. The protocol is as follows:

EXPERIMENT 4.—A dog weighing 11.65 Kg. was used. The following data were obtained:

| Date | Blood Pressure | Nonprotein Nitrogen | Creatinine | "Guanidine" | Comment |
|---|---|---|---|---|---|
| 12/12/38 | 115 | | | | |
| 12/13/38 | 80 | 22.8 | 1.2 | 0.4 | Right nephrectomy; clamp on left renal vein |
| 12/14/38 | 70 | 70 | 3.2 | 0.5 | |
| 12/15/38 | 95 | 147 | 6 | 1.143 | |
| 12/16/38 | | | | | Dog found dead |

In this experiment there was no increase in the systolic blood pressure, although there were marked retention of nitrogen and a great increase in the "guanidine" content of the blood

In the 2 following experiments both kidneys were removed and the effect upon the blood pressure and the "guanidine" content of the blood noted.

EXPERIMENT 5.—A dog weighing 12.7 Kg. was used. The left kidney was removed Dec. 20, 1938.

| Date | Blood Pressure | Nonprotein Nitrogen | Creatinine | "Guanidine" | Comment |
|---|---|---|---|---|---|
| 12/30/38 | 80 | | | | |
| 12/31/38 | 75 | | | | |
| 1/ 3/39 | 100 | 42 | 2.1 | 0.19 | |
| 1/ 4/39 | 70 | 77.9 | 3.6 | 0.87 | Right kidney removed |
| 1/ 5/39 | 90 | 150 | 9.6 | 0.92 | |
| 1/ 6/39 | 130 | 194 | 12 | 0.82 | |
| 1/ 7/39 | 135 | 220 | 20 | 1.34 | |
| 1/ 9/39 | 135 | 289 | 25 | 1.54 | |
| 1/10/39 | 90 | 306 | 26 | 1.36 | |
| 1/11/39 | 110 | 325 | 27.7 | 2.16 | |
| 1/12/39 | 125 | 375 | 32.7 | 2.08 | |
| 1/13/39 | | | | | Dog died |

EXPERIMENT 6.—A dog weighing 9.8 Kg. was used. The dog was operated on April 30, 1936, at which time both renal arteries were partially constricted with Goldblatt clamps. The blood pressure was elevated from April 30 to July 17, varying from 190 to 270 millimeters of mercury. The range of blood pressure from December 8 until Dec. 20, 1938, was 150 to 180 millimeters of mercury. The following data were obtained:

| Date | Blood Pressure | Nonprotein Nitrogen | Creatinine | "Guanidine" | Comment |
|---|---|---|---|---|---|
| 12/20/38 | 160 | 26 | 1.3 | 0.54 | |
| 12/21/38 | 110 | 22 | 1.3 | 0.67 | Left kidney removed |
| 12/22/38 | 160 | 22 | 1.3 | 0.24 | |
| 12/23/38 | 150 | 18.5 | 1.2 | 0.174 | |
| 12/25/38 | 160 | | | | |
| 12/30/38 | 170 | | | | |
| 12/31/38 | 195 | 21 | 1.2 | 0.197 | |
| 1/ 3/39 | 165 | 26 | 1.6 | 0.183 | |
| 1/ 4/39 | 110 | 76.9 | 2.9 | 0.87 | Right kidney removed |
| 1/ 5/39 | 115 | 146 | 6.4 | 0.87 | |
| 1/ 6/39 | | | | | Dog died |

Experiment 6 was especially interesting, since the animal had elevation of blood pressure for more than two years and showed definite hypertension at the beginning of the experiment. After removal of both kidneys, although the "guanidine" content of the blood increased rapidly, the blood pressure actually fell lower than it had been in two years.

In experiments 4 and 5 there was a marked increase in the "guanidine" content of the blood without any elevation in blood pressure.

We have also attempted to establish the identity of the substance in the blood which we have provisionally designated as "guanidine." This problem was studied by producing severe "uranium nephritis" with renal insufficiency in dogs. After the values for creatinine and "guanidine" had become very high, the dogs were killed and the entire amount of blood was removed. In all, 20 dogs were employed; approximately 25 liters of blood was obtained, from which 150 liters of filtrate was studied. The nephritis was produced by giving the animals uranium nitrate in doses of 20 mg. per kilogram of body weight. The dogs when killed showed values for blood creatinine varying from 15 to 16 mg. per hundred cubic centimeters.

In an attempt to isolate the "guanidine," we have employed tungstic acid filtrates of blood from dogs in the last stages of "uranium nephritis." These filtrates were extracted with Lloyd's reagent and an eluate prepared from it, by means of a saturated barium hydroxide solution. We have found that "guanidine" is precipitated from these eluates by phosphotungstic acid or by trinitrophenol. The precipitation is more complete with trinitrophenol if potassium chloride is also added. Thus far we have been unable to separate it from creatinine.

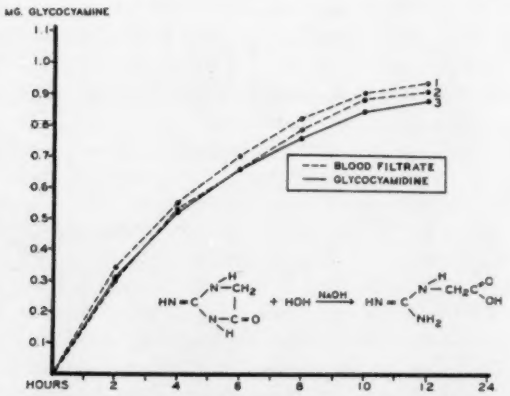
The similarity of the color given by these more concentrated solutions with the ferricyanide-nitroprusside reagent to that given by a solution of glycocyamidine is striking. In fact, it is difficult to compare this color in the colorimeter with that of any of the guanidine bases or their derivatives (such as arginine, glycocyamine or creatinine) except glycocyamidine. This similarity in color value is present with all concentrations.

We found in previous work that norit (a prepared charcoal) and Lloyd's reagent (a specially prepared siliceous earth) would absorb simple guanidine bases from the aqueous solutions and that these bases are readily released from norit by means of acid alcohol, an average of 80 to 90 per cent of guanidine bases being released after this treatment. We have also found that the simple guanidine bases are released from Lloyd's reagent by means of barium hydroxide solution only to the extent of approximately 30 per cent of the absorbed amount. We have therefore compared the amount released from norit and Lloyd's reagent extracts of the tungstic acid filtrates of dog blood, acid alcohol

being employed to produce release from norit and barium hydroxide to produce release from Lloyd's reagent (table).

*Comparison of the Color Values of Norit and Lloyd's Reagent Extract with Use of the Alkaline Nitroprusside Ferricyanide Reagent (Methylguanidine Employed as Standard)*

| No. | Guanidine Bases with Lloyd's Reagent Extract, Mg. per 100 Cc. | Guanidine Bases with Norit Extract, Mg. per 100 Cc. | Comment |
|---|---|---|---|
| 1 | 0.81 | 0.84 | Normal dog blood |
| 2 | 0.88 | 0.74 | Normal dog blood |
| 3 | 1.11 | 2.27 | 2 mg. methylguanidine added |
| 4 | 1.30 | 2.24 | 2 mg. guanidine added |
| 5 | 4.18 | 4.32 | Uranium nephritis (N. P. N. 300) |
| 6 | 3.95 | 3.48 | Uranium nephritis (N. P. N. 225) |




Increase in intensity of Sakaguchi reaction.

If the increase in color in experiments 5 and 6 was due to simple guanidine bases, the value for the Lloyd's reagent extracts should have been approximately 2.1 mg. instead of 4.18 and 3.95 mg. This observation is strong evidence against this compound being a simple guanidine base.

We have also studied the question whether this increase in color, which we have designated as due to increased "guanidine," is due to a substance normally present in dog blood. Normal dog blood before treatment with arginase gives an appreciable color varying from that indicating 0.4 mg. to that indicating 0.8 mg. of guanidine per hundred cubic centimeters. The major part of this color is removed by treatment with arginase. After such treatment there remains a small amount of color, representing a value of 0.1 mg. to 0.2 mg. of methyl guanidine per hundred cubic centimeters. This observation, which has

been repeated many times, indicates that most of the color attributed to the presence of "guanidine" in dog blood is really due to arginine. The substance present in the blood of dogs with "uranium nephritis" is not reduced in amount by treatment with arginase, which would seem good reason to believe that it is not arginin.

We have made studies regarding the behavior of this substance toward Sakaguchi's reagent. This reagent, as is well known, is apparently specific for guanidine compounds containing one group substitution. Normal dog blood with norit extract or Lloyd's reagent gives a well marked Sakaguchi reaction. After treatment of the blood with arginase, however, the color produced is reduced approximately 90 per cent. The intensity of Sakaguchi's reaction was not increased in our experiments after the dogs showed marked renal insufficiency. The guanidine-like substance which is increased in the blood of these dogs with renal insufficiency does not give a positive Sakaguchi reaction.

We have found that the substance referred to as "guanidine" is precipitated by phosphotungstic acid and trinitrophenol. Complete separation from creatinine has not been achieved. We have found that solutions of this substance obtained from the blood in the presence of renal insufficiency when made alkaline and allowed to stand show a gradual increase in intensity of the Sakaguchi reaction. The increase in color is at a rate similar to that produced in a solution of glycocyamidine similarly treated (see chart). These observations indicate that the substance is a guanidine derivative of an anhydride type and that under alkaline treatment the guanidine ring opens and the resulting compound gives a Sakaguchi reaction.

## CONCLUSIONS

1. The increase in "guanidine" in the blood in experimental renal insufficiency occurs both with and without accompanying hypertension.

2. The compound which we have designated as "guanidine" is apparently a guanidine derivative of an anhydride type and may be glycocyamidine.

# MULTIPLE MYELOMA

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The problem of the cytologic origin and relation of multiple myeloma has been one of the puzzles of medicine ever since Macintyre [1] reported the first case nearly a hundred years ago. There are indications that the problem is approaching a solution. It is hoped that the following report of a case, particularly the correlation of its many interesting features with those reported in the literature, may contribute to a better understanding of the disease.

## REPORT OF A CASE

A. W. R., a chemist aged 55, was admitted in October 1934 to the Massachusetts Memorial Hospitals, with weakness as the most prominent symptom. The historical data included fracture of the right tibia as a result of a fall in 1923, paracentesis of the left ear drum in 1928, "septic" throat in 1930 and many migrainous headaches, which had become much less severe in recent years.

About six months before entering the hospital he had experienced a "sensation of adhesions in the right side of the chest." Shortness of breath, progressive fatigability and a hacking cough came on three months later. The cough interfered with sleep. The muscles of the neck felt stiff; headache was produced by stretching either side of the neck. Sore mouth, loss of appetite, nausea, slight recurrent attacks of diarrhea and flatulence developed. A month later he noticed a firm, somewhat tender tumor in the left testicle. A persistent nasal discharge appeared, with intermittent pain and discomfort in the antrums, especially the left.

The patient was well developed and slightly obese. The greatest weight, several years ago, had been 210 pounds (95.2 Kg.); at the time of admission to the hospital he weighed 188 pounds (85.3 Kg.). The skin had a yellowish pallor. The tongue was coated and the breath foul. There were shallow ulcerations of the gums and many dental fillings. Moist rales were heard throughout the lungs, especially in the upper lobe of the right. The heart was normal. The pulse rate was 82, the blood pressure 148 systolic and 84 diastolic and the temperature 99 F. The liver, spleen and kidneys were not felt. There were several small firm nodules in the left testicle.

The urine contained a large amount of albumin, a few leukocytes and erythrocytes and a number of hyaline, finely and coarsely granular and epithelial casts. Bence Jones protein was not found. Examination of the blood revealed marked anemia of the hypochromic type. The Wassermann, the Kahn and the Hinton reactions were negative. The icteric index was 7, the bleeding time six minutes, the clotting time (Lee and White) nine minutes and clot retraction normal. Other

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From the Evans Memorial of the Massachusetts Memorial Hospitals and the Boston University School of Medicine.

1. Macintyre, W.: A Case of Mollities and Fragilitas Ossium, Accompanied with Urine Strongly Charged with Animal Matter, Med.-Chir. Tr. **33**:211, 1850.

hematologic data are shown in the table. Occult blood was found in the feces. The Takata-Ara reaction was positive. Two Aschheim-Zondek tests gave negative results.

An electrocardiogram was normal. The basal metabolic rate was + 5 per cent. Roentgenograms revealed an old fracture of the lower part of the right tibia, with hypertrophic changes about the ankle. The skeleton showed nothing suggesting multiple myeloma. (In a film of the skull made at the time of necropsy a few small "punched-out" areas of rarefaction could be seen.) Films of the scrotum showed a small dense shadow suggesting calcareous deposition in a teratoma. (This finding led to the performance of the previously mentioned Aschheim-Zondek tests.)

The left testicle was removed for examination. It contained several small tumors made up chiefly of cells having the appearance of atypical plasma cells.

*Hematologic Data*

| | Date (1934) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10/30 | 11/1 | 11/6 | 11/8 | 11/9 | 11-13 | 11/17 | 11/26 | 11/28 | 11/30 | 12/3 | 12/5 |
| Red cells (millions) | 2.15 | ... | 1.57 | 1.35 | ... | 1.55 | 2.33 | 2.63 | 2.76 | 2.41 | 1.8 | ... |
| Hemoglobin, % | 39 | ... | 35 | 30 | ... | 33 | 45 | 50 | 50 | 47 | 35 | ... |
| Leukocytes (thousands) | 11.4 | ... | 10 | 7.3 | ... | 9.8 | ... | 9.9 | 7.3 | 6.5 | 6.4 | ... |
| Neutrophils | 42 | ... | 40 | 48 | ... | 52 | 48 | 50 | 60 | 54 | 67 | ... |
| Lymphocytes | 38 | ... | 20 | 13 | .. | 28 | 35 | 39 | 30 | 40 | 26 | ... |
| Myelocytes and myeloblasts | 5 | ... | 19 | 12 | ... | 10 | 9 | 6 | 3 | 2 | 5 | ... |
| "Plasma cells" | 8 | ... | 5 | 10 | . . | 2 | 5 | 3 | 1 | 1 | 0 | ... |
| Doubtful forms | ... | ... | 10 | 12 | ... | ... | ... | ... | ... | ... | Few | ... |
| Serum protein, % | ... | 10.6 | ... | 13 | ... | ... | ... | ... | ... | ... | 14.9 | ... |
| Serum albumin, % | ... | 2.2 | ... | 3 | ... | ... | ... | ... | ... | ... | 3.1 | ... |
| Serum globulin, % | ... | 8.4 | ... | 10 | ... | ... | ... | ... | ... | ... | 11.8 | ... |
| Serum calcium, mg. per 100 cc. | ... | 9.9 | ... | . . | 10 | ... | 9.4 | ... | ... | ... | ... | ... |
| Serum phosphorus, mg. per 100 cc. | ... | 4.2 | ... | ... | 7.5 | ... | ... | ... | ... | ... | ... | ... |
| Nonprotein nitrogen, mg. per 100 cc. | ... | ... | ... | ... | ... | ... | ... | ... | ... | 101 | 185 | 240 |

The cytoplasm was basophilic in many of them; the nucleus was eccentric in some, and a perinuclear *Hof* was present in a few. The chromatin, however, only rarely showed a tendency to radial arrangement. Some of the cells appeared definitely to be young myeloid cells (stem cells, lymphoidocytes and premyelocytes), with their characteristic nucleoli. Several mitoses were seen.

The patient was transferred to the Collis P. Huntington Memorial Hospital for roentgen treatment. During his stay there his symptoms gradually increased in severity. The weakness became extreme; nausea was constant, and all food caused vomiting. Bleeding from the gums and nose became troublesome. Many spirella and fusiform bacilli were found in smears from the gums. The temperature rose to 104 F. At no time was pain of importance, except for occasional headache. The urine persistently contained large amounts of albumin, a variable number of casts and traces of pus and blood. During the last few days of life there was marked oliguria. Repeated tests for Bence Jones protein gave negative results.

Treatment consisted of five blood transfusions of 300 to 500 cc. each and small doses of high voltage roentgen radiation and radium, applied to the thighs, pelvis and sternum. There was no evidence that these measures had any beneficial results, except for a temporary increase in the number of red blood cells after each transfusion. The patient finally became irrational and comatose and died five weeks after admission to the hospital, four months after the onset of symptoms.

Necropsy was performed by Dr. Shields Warren. There follows an abstract of his report:

The lymph nodes were not palpable. The liver extended 5 cm. below the costal margin. The lungs contained a few small discrete dark red or grayish foci of bronchopneumonia. The spleen weighed 380 Gm. and the liver 2,120 Gm. The capsule of the kidneys stripped readily from a smooth grayish white surface. The renal medulla and cortex were not clearly demarcated. Both kidneys were pale; the glomeruli were not visible. The left testicle had been removed; the right was infiltrated in its lower anterior third with a firm grayish yellow tumor, which faded indefinitely into the surrounding testicular substance and penetrated slightly the overlying tunica. The femur, vertebrae, ribs and sternum contained pale yellow or yellowish red marrow of uniform texture. Bony trabeculation was normal. The skull could be sawed with remarkable ease, but there was no other definite evidence of softening. The cranial bone was only 0.2 to 0.4 cm. thick, with almost complete absence of diploe. When the removed portion of the skull was held up to the light, reddish areas suggesting hemopoiesis were seen. They corresponded roughly to the rarefied areas seen in roentgenograms taken post mortem.

*Microscopic Examination.*—Spleen: The normal structure was obliterated. The follicles had almost entirely disappeared, and the sinusoidal structure was seen in only a few parts. Large numbers of immature but not clearly identified blood cells filled the sinuses and reticulum. Most of these cells showed basophilic, slightly gr. ular cytoplasm, with a central or eccentric vesicular nucleus, often with a single, prominent nucleolus. Mitotic figures were relatively rare.

Kidney: The majority of the glomeruli were swollen and edematous, and occasionally one was adherent to the capsule. There were one or two sclerosed glomeruli. The tubules were separated by a fairly uniform increase in the fibrous tissue of the stroma. The epithelium, especially of the proximal convoluted tubules, showed slight to marked albuminous degeneration. Some of the tubules contained polymorphonuclear leukocytes and others hyaline casts. Clusters of immature blood cells were present between the tubules. They were for the most part of the granulocytic series, though a few lymphocytes and plasma cells were seen. Neutrophilic and eosinophilic myelocytes, premyelocytes and cells similar to those seen in the spleen and testis could be definitely identified. Mitoses were frequent.

Testis: There was diffuse cellular infiltration of interstitial tissue, varying from wide separation of tubules to the presence of only scattered cells (figs. 1 and 2). The infiltrating cells were fairly uniform and discrete; there was no supporting stroma or increased vascularity. The cells ranged from 5 to 10 microns in diameter, most of them being about 8 microns. They were rounded or polyhedral, with a tendency to mosaic patterning. The cytoplasm was usually basophilic, opaque and finely granular, with occasionally a clearer crescent adjacent to the eccentric nucleus. The nucleus was round or oval, with clearcut blocklike distribution of chromatin and a well marked nuclear membrane. Among these cells were rare somewhat larger ones with a large vesicular nucleus and scattered neutrophilic and eosinophilic granules. With Unna's stain many of the smaller

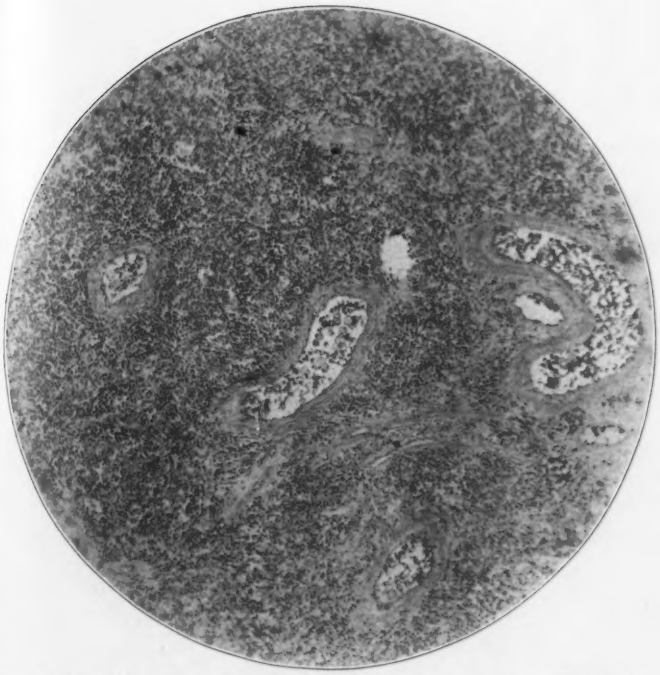

Fig. 1.—Low magnification of section of myelomatous tumor of the testis.

Fig. 2.—Invasion of myeloma cells of stroma between seminiferous tubules.

cells showed a rose cytoplasm. This picture was identical with that seen in the surgically removed testis (fig. 3).

Bone Marrow: A portion of the marrow was fatty; the remainder was completely filled by fairly uniform masses of cells. Most of the cells were of immature type, with a large, somewhat vesicular type of nucleus and a prominent

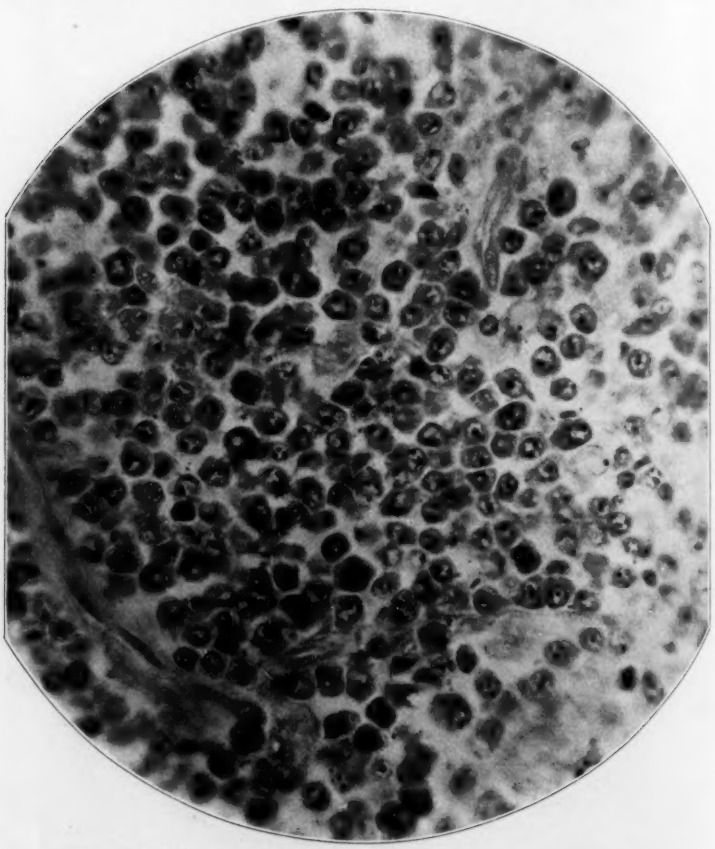

Fig. 3.—High magnification of testicular tumor, showing mitoses.

nucleolus. The cytoplasm was scanty and somewhat basophilic. No granules were seen. In some portions there were neutrophilic and eosinophilic myelocytes. The reticuloendothelial cells were not remarkable.

Dr. Warren wrote in his summary: "This case is most obscure, and the final diagnosis is still somewhat uncertain." He expressed the belief that aleukemic myeloblastic leukemia had to be considered. The identity of the abnormal cells was not, he stated, established with certainty, although subsequent study convinced him that they were plasma cells.

I had assumed that the cells found ante mortem in the peripheral blood of this patient were atypical plasma cells such as had been reported in a number of cases of multiple myeloma by other authors. A few myelocytes and myeloblasts also were present in the blood, and these too had been observed in several reported cases of myeloma (fig. 4). Because of the uncertain status of the tumor cells,

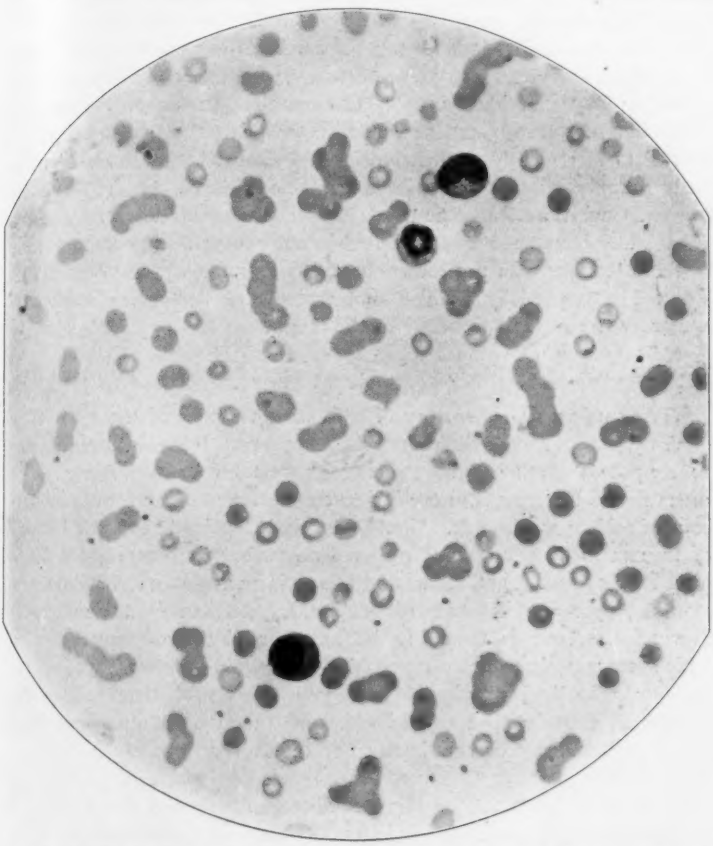

Fig. 4.—Blood film, showing neutrophilic myelocyte (top) and myeloma cell (below).

sections of the testicular tumors were submitted by Dr. Warren to a number of pathologists [2] for their opinions. There was general agreement that the neoplastic cells, like those observed in the blood, were plasma cells of an atypical form. The

2. Drs. C. F. Branch, F. Stewart, C. F. Geschickter, F. Parker, R. H. Jaffé, Hal Downey, William Bloom and R. P. Custer.

diagnosis of multiple myeloma of the so-called plasma cell type appeared, therefore, to be justified.

Although Wallgren [3] has pointed out that different authors have used different criteria for the diagnosis of multiple myeloma, the present generally held conception is of a multiple tumor of bone marrow, or a diffuse hyperplasia, consisting usually of cells resembling plasma cells. Geschickter and Copeland [4] gave six cardinal diagnostic clinical signs of multiple myeloma, usually present "collectively or in pairs or triads in any individual case": (1) multiple tumor of the skeletal trunk in a person who is more than 35 years old; (2) pathologic fracture of a rib; (3) Bence Jones proteinuria; (4) lumbar backache and signs of early paraplegia; (5) otherwise unexplained anemia, and (6) chronic nephritis with azotemia and low blood pressure. Later, however, Geschickter [5] reported a case of multiple myeloma that presented none of these features. In my case only points 5 and 6 were fully satisfied. Point 1 was partially fulfilled, but the site of demonstrable skeletal tumors was the skull rather than the trunk.

### TRAUMA

The patient gave a history of a fall and fracture of the right tibia eleven years before the clinical onset of myeloma. It seems unreasonable to suppose that there was an etiologic relation between them. The interval was too long, and the incidence of trauma of some sort in persons of middle age is high. Geschickter and Copeland [4] found a history of trauma in 20 per cent of reported cases, but they expressed doubt as to its significance and stated that "there is no evidence at hand to substantiate preceding fracture of healthy bone as an etiologic factor." Nevertheless, one is bound to be impressed by the frequency with which trauma has been reported as initiating the symptoms in patients who had previously felt well. I doubt that it can be eliminated entirely as a causative factor, although in most cases the injury undoubtedly occurred after the disease had already begun. It is of interest to refer to a medicolegal case [6] in which damages were awarded on the basis of the jury's verdict that myeloma developed as a result of an injury and was the cause of death eight months later.

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3. Wallgren, A.: Untersuchungen über die Myelomkrankheit, Upsala läkaref. förh. **25**:113, 1920.

4. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, Arch. Surg. **16**:807 (April) 1928.

5. Geschickter, C. F.: Multiple Myeloma as a Single Lesion, Ann. Surg. **92**: 425, 1930.

6. Myeloma Attributed to Trauma, Medicolegal Reports, J. A. M. A. **97**:415 (Aug. 8) 1931.

### PAIN

In most of the published reports pain was the outstanding symptom of multiple myeloma. In the present instance pain that could be ascribed directly to the myeloma was absent. The patient complained at times of headache, to which he had been subject in greater degree before (for many years) than after the myeloma appeared; also, he had slight pain in the antrum of Highmore, which was believed to have been the result of infection and congestion of the sinuses and not a direct result of the major disease.

Pain is apparently less likely to be a prominent symptom when, as in this case, there is diffuse involvement of the marrow,[7] or when the tumor is situated in tissue without skeletal involvement.[8]

A compilation of the incidence of pain, of clinically recognized tumor, of roentgen evidence of the disease and of Bence Jones proteinuria in 259 cases of multiple myeloma, selected because the histories were given with sufficient clarity regarding each of these items, shows that absence of pain was rare (4.6 per cent); clinical recognition of the tumor was much less frequent (36.7 per cent) than roentgen evidence of it (96.9 per cent), and Bence Jones protein could not be detected in a substantial proportion of the cases (38.2 per cent).

### BENCE JONES PROTEINURIA AND RENAL LESION

In 1930 Perla and Hutner[9] reported a case which, according to Bell,[10] "is the only case in the literature of proved renal insufficiency in a myeloma without Bence-Jones proteinuria." The case presented here appears to be another; a renal lesion was indicated by gross albuminuria, cylindruria and an ultimate increase of the nonprotein nitrogen content of the blood to 240 mg.

Marked albuminuria without Bence Jones proteinuria appears to be unusual in cases of multiple myeloma. Magnus-Levy[11] expressed the

7. (*a*) Diffuse Multiple Myeloma, Cabot Case 21082, New England J. Med. **212**:353, 1935. (*b*) Foord, A. G., and Randall, L.: Hyperproteinemia, Autohemagglutination and Renal Insufficiency in Multiple Myeloma, Am. J. Clin. Path. **5**:532, 1935.

8. (*a*) New, G. B., and Harper, F. R.: Plasma Cell Myeloma of the Pharynx and Cervical Region Without Skeletal Involvement, Arch. Otolaryng. **16**:50 (July) 1932. (*b*) Jackson, H., Jr.; Parker, F., Jr., and Bethea, J. M.: Studies of Diseases of the Lymphoid and Myeloid Tissues: II. Plasmatocytomata and Their Relation to Multiple Myelomata, Am. J. M. Sc. **181**:169, 1931.

9. Perla, D., and Hutner, L.: Nephrosis in Multiple Myeloma, Am. J. Path. **6**:285, 1930.

10. Bell, E. T.: Renal Lesions Associated with Multiple Myeloma, Am. J. Path. **9**:393, 1933.

11. Magnus-Levy, A.: Ueber die Myelomkrankheit: III. Vom Stoffwechsel; die Bence-Jones Proteinurie, Ztschr. f. klin. Med. **119**:307, 1932.

view that massive albuminuria in this disease is due chiefly to the presence of Bence Jones protein, and that reports of its absence when large amounts of albumin are present in the urine were erroneous. He claimed that the Bence Jones bodies were overlooked, owing to the fact that they may be insoluble under certain conditions in boiling urine, especially when present in large amounts. Bloch,[12] Hopkins and Savory [13] and Berglund and Medes [14] called attention to the difficulties that may be encountered in testing for these proteins and stated that their solubility at the boiling point depends to an important degree on the relation of salts to acids in the solution. The investigations of Bayne-Jones and Wilson,[15] supported by Robinson's [16] studies, indicated that "Bence-Jones protein is not a single substance, but . . . a group of similar, but not identical proteins," and that this complexity may have a bearing on the difficulties of determining its presence under certain circumstances. Magnus-Levy [17] therefore estimated the incidence of Bence Jones proteinuria with multiple myeloma to be about 80 per cent rather than 65 per cent, as given by Geschickter and Copeland.[18]

In the present case tests for Bence Jones protein gave persistently negative results. Furthermore, the microscopic examination of the kidneys (fig. 5) revealed nothing resembling the histologic changes which Forbus and his associates [19] regarded as characteristic of renal damage resulting from excretion of Bence Jones protein.[20] Feller and Fowler [21]

12. Bloch: Ein Beitrag zur Klinik und Diagnose des multiplen Myleoms, Folia haemat. **26**:119, 1921.

13. Hopkins, F. G., and Savory, H.: A Study of Bence-Jones Protein, and of the Metabolism in Three Cases of Bence-Jones Proteinuria, J. Physiol. **42**: 189, 1911.

14. Berglund, H., and Medes, G.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935.

15. Bayne-Jones, S., and Wilson, D. W.: Immunological Reactions of Bence-Jones Proteins: I. Differences Between Bence-Jones Proteins and Human Serum Proteins, Bull. Johns Hopkins Hosp. **33**:37, 1922.

16. Robinson, S. H. G.: An Investigation of the Antigenic Properties of Four Specimens of Bence-Jones Protein Obtained from Cases of Myelomatosis, Brit. J. Exper. Path. **8**:454, 1927.

17. Magnus-Levy, A.: Ueber die Myelomkrankheit: VI. Beiträge zur Klinik und Pathologie, Ztschr. f. klin. Med. **121**:533, 1932.

18. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, ed. 2, New York, American Journal of Cancer, 1936.

19. Forbus, W. D.; Perlzweig, W. A.; Parfentjev, I. A., and Burwell, J. C., Jr.: Bence-Jones Protein Excretion and Its Effects on the Kidney, Bull. Johns Hopkins Hosp. **57**:47, 1935.

20. Dr. Forbus examined a section of the kidney and agreed "that the picture is not that which I have described in cases of Bence Jones proteinuria."

21. Feller, A. E., and Fowler, W. M.: Hyperproteinemia in Multiple Myeloma, J. Lab. & Clin. Med. **23**:369, 1938.

and Barfield-Carter [22] reported cases of marked albuminuria, but Bence Jones protein was never detected.

Thannhauser and Krauss [23] and subsequent authors, notably Perla and Hutner,[9] expressed the belief that the nephropathy of multiple myeloma is a form of nephrosis. Ehrich,[24] however, came to the conclusion that it is a question not of epithelial degeneration leading to tubular destruction (nephrosis) but of plugging of the tubules with casts

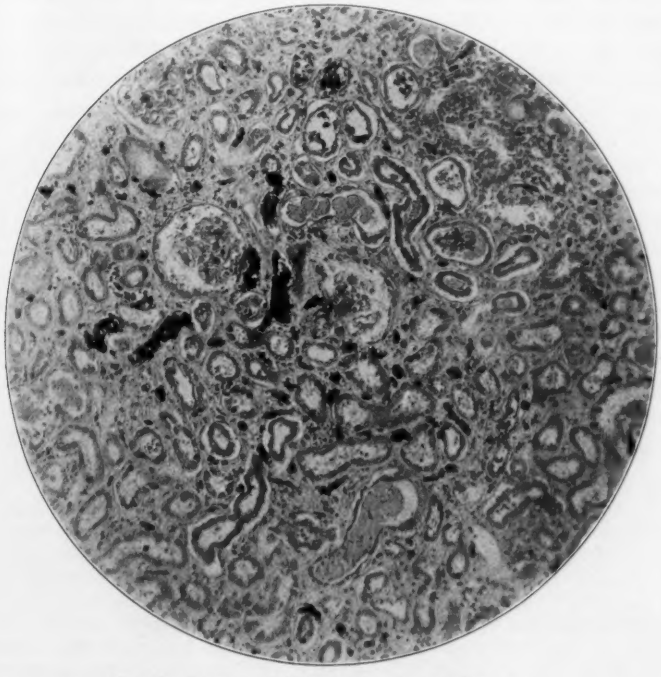

Fig. 5.—Section of kidney, showing hyaline casts.

of Bence Jones protein and subsequent hydronephrotic atrophy. Bell [10] stated:

> The only direct effect of multiple myeloma on the kidneys is due to the formation of tubular casts of Bence-Jones protein that obstruct the tubules.

22. Barfield-Carter, M.: Multiple Myeloma and Associated Renal Lesions, Am. J. Roentgenol. **36**:830, 1936.

23. Thannhauser, S. J., and Krauss, E.: Ueber eine degenerative Erkrankung der Harnkanälchen (Nephrose) bei Bence-Jones'scher Albuminurie, Deutsches Arch. f. klin. Med. **133**:183, 1920.

24. Ehrich, W.: Die Nierenerkrankung bei Bence-Jonesscher Proteinurie, Ztschr. f. klin. Med. **121**:396, 1932.

Casts were not found in the 2 cases of his series in which no Bence Jones protein was excreted. This explanation was not accepted as wholly satisfactory by Buschke,[25] and Randerath [26] concluded that his experiments contradicted the observations of Ehrich and justified the inclusion of the renal changes among the nephroses.

Bell [10] wrote that "none of the authors mentions hematuria in a case of multiple myeloma." That is true in regard to gross hematuria, but there have been several reports [27] of the observation of blood by microscopic examination, and in Lewis' [28] case the hematuria was sufficiently profuse for the patient himself to be aware of it. A few red disks were present in a number of the urinary specimens voided by my patient.

### HYPERPROTEINEMIA

An increase of the total protein in the blood plasma or serum in cases of multiple myeloma has been reported by a number of observers. Schumacher, Williams and Coltrin [29] reported the huge amount of 23.29 per cent. That a high serum protein level is a valuable diagnostic finding is substantiated by Jeghers and Selesnick,[30] who reported that of 13 cases of hyperproteinemia observed in recent years at the Boston City Hospital 7 were instances of multiple myeloma; in the others the protein

25. Buschke, F.: Urämie bei Bence-Jonesscher Albuminurie, Klin. Wchnschr. **11**:408, 1932.

26. Randerath, E.: Pathologisch-anatomische und experimentelle Untersuchungen zur Frage der Nierenveränderungen bei Bence-Jonesscher Proteinurie, Ztschr. f. klin. Med. **127**:527, 1934.

27. (*a*) Wintrobe, M. M., and Buell, M. V.: Hyperproteinemia Associated with Multiple Myeloma, Bull. Johns Hopkins Hosp. **52**:156, 1933. (*b*) Sweigert, C. F.: Multiple Myeloma with Hyperproteinemia, Am. J. M. Sc. **190**:245, 1935. (*c*) Bannick, E. G., and Greene, C. H.: Renal Insufficiency Associated with Bence-Jones Proteinuria: Report of Thirteen Cases with Note on Changes in Serum Protein, Arch. Int. Med. **44**:486 (Oct.) 1929. (*d*) Gros, W.: Zur Frage gesetzmässiger Veränderungen des Bluteiweissbildes beim multiplen Myelom, Deutsches Arch. f. klin. Med. **177**:461, 1935. (*e*) Weinberg, F., and Schwarz, E.: Die Klinik und pathologische Anatomie des multiplen Myeloms, Virchows Arch. f. path. Anat. (supp.) **227**:88, 1920. (*f*) Perlzweig, W. A.; Delrue, G., and Geschickter, C.: Hyperproteinemia Associated with Multiple Myelomas: Report of an Unusual Case, J. A. M. A. **90**:755 (March 10) 1928. (*g*) Patek, A. J., and Castle, W. B.: Plasma Cell Leukemia, Am. J. M. Sc. **191**:788, 1936. (*h*) Kleine, H. O.: Kristalloide Riesenzellen in Harnkanälchen bei plasmazellulärem Myelom, Beitr. z. path. Anat. u. z. allg. Path. **79**:678, 1928.

28. Lewis, D.: Multiple Myeloma, Internat. Clin. **1**:157, 1927.

29. Schumacher, I. C.; Williams, O. O., and Coltrin, G. S.: Plasma Cell Myeloma and Hyperproteinemia, California & West. Med. **47**:174, 1937.

30. Jeghers, H., and Selesnick, S.: Hyperproteinemia: Its Significance, Internat. Clin. **3**:249, 1937.

content of the blood never exceeded 9 per cent, whereas in the cases of multiple myeloma it varied between 9.4 and 12.2 per cent. Although it is true, as Bing [31] wrote, that "in most cases hyperproteinemia will be a sign of myelomatosis," it must be remembered that the symptom may occur with a few other diseases, notably with kala-azar and lymphogranuloma venereum, and occasionally leprosy and cirrhosis of the liver.

In the present case the highest serum protein value was 14.9 per cent, of which 11.8 per cent was globulin and only 3.1 per cent albumin. Evidently the hyperproteinemia was purely hyperglobulinemia, just as it was in other cases reported.

In contrast to other writers, Chester [32] reported a low serum protein level in 2 cases of multiple myeloma. He expressed the belief that the total protein of the blood plasma diminished in the late stages of the disease and that hypoproteinemia would ensue if the patients were observed long enough. Feller and Fowler [21] were unable to confirm this; and in my case, as well as in Sweigert's,[27b] the highest amounts were found shortly before death.

Freund and Magnus-Levy [33] stated that excretion of Bence Jones protein in the urine is accompanied with a low or normal total amount of protein in the blood plasma. Conversely, as pointed out by Cantarow,[34] Bence Jones protein has been found only rarely in the presence of hyperproteinemia. Nielsen,[35] for example, reported 4 cases, 2 of hyperproteinemia without Bence Jones bodies in the urine and 2 of hypoproteinemia with abundant Bence Jones protein. Several other authors,[36] however, have reported the coexistence of Bence Jones proteinuria and hyperproteinemia; and one of Gross and Vaughan's [37] patients had normal blood protein but no Bence Jones protein in the

31. Bing, J.: Some Cases of Hyperproteinemia, Acta med. Scandinav. **88**: 478, 1936.

32. Chester, W.: Multiples Myelom und Hypoproteinämie, Ztschr. f. klin. Med. **124**:466, 1933.

33. Freund, R., and Magnus-Levy, A.: Multiple Myeloma: V. Ueber Besonderheiten der Blutzusammensetzung, Ztschr. f. klin. Med. **121**:1, 1932.

34. Cantarow, A.: Bence-Jones Proteinemia in Multiple Myeloma, Am. J. M. Sc. **189**:425, 1935.

35. Nielsen, H. E.: Four Cases of Myelomatosis, Hospitalstid. **81**:549, 1938.

36. (*a*) Stewart, A., and Weber, F. P.: Myelomatosis, Quart. J. Med. **7**: 211, 1938. (*b*) Decherd, G. M., and Holland, L.: Multiple Myeloma with Hyperglobulinemia, J. Trop. Med. **41**:129, 1938. (*c*) Shirer, J. W.; Duncan, W., and Haden, R. L.: Hyperproteinemia Due to Bence-Jones Protein in Myelomatosis, Arch. Int. Med. **50**:829 (Dec.) 1932. (*d*) Feller and Fowler.[21]

37. Gross, R. E., and Vaughan, W. W.: Plasma Cell Myeloma: Report of Two Cases with Unusual Survivals of Six and Ten Years, Am. J. Roentgenol. **39**:344 (March) 1938.

urine. My case was similar in this respect to the first 2 of Nielsen's cases: The blood protein level was increased, and Bence Jones protein was absent.

### CALCIUM AND PHOSPHORUS

The serum calcium level has been reported high in a number of cases of multiple myeloma, with serum phosphorus normal or slightly elevated. This relation, although present in only some of the cases, serves to differentiate multiple myeloma from hyperparathyroidism. According to Gutman and Gutman,[38] the hypercalcemia is not brought about by a mere increase of the calcium bound to an excess of globulin but is the result of destruction of bone by the neoplasm. Serum calcium in my case was normal (9.9 and 10 mg. per hundred cubic centimeters on two determinations), despite an excess of serum globulin, but phosphorus was increased (4.2 and 7.5 mg. per hundred cubic centimeters). In this my case was similar to several other reported cases.[39] Low serum phosphorus and high calcium, however, a combination that is typical of hyperparathyroidism, may rarely be found with multiple myeloma.[40]

### EXTRAOSSEOUS MYELOMA

The most striking feature of the case reported here was the presence of testicular tumors without other extraosseous involvement.

Geschickter and Copeland [4] in their review of all cases reported before 1928 did not mention metastases in the testicles [41]; neither did Magnus-Levy [17] or Wallgren,[8] both of whom cited numerous authors in their articles. In an extensive survey of the literature on multiple myeloma I have seen only one mention of a testicular tumor. This was in a case referred to by Porchownik [42] as having been observed by Werzberg in Russia. Large round nodules were found in the testis at necropsy. Other details about the case were not given, so that doubt exists as to the diagnosis of myeloma. In Ghon and Roman's [43] case

38. Gutman, A. B., and Gutman, E. B.: Calcium-Protein Relation in Hyperproteinemia: Total and Diffusible Serum Calcium in Lymphogranuloma Inguinale and Myeloma, Proc. Soc. Exper. Biol. & Med. **35**:511, 1936.

39. Howard, C.: X-Ray Aspects of Endotheliosis, read before the Eleventh Annual Fortnight of the New York Academy of Medicine, Oct. 27, 1938. Multiple Myeloma, Cabot Case 21052, New England J. Med. **212**:204, 1935. Forbus and others.[19] Cantarow.[34]

40. Multiple Plasma Cell Myeloma, Cabot Case 23171, New England J. Med. **216**:757, 1937.

41. The case to which they referred briefly in the revised edition of their book [18] is the one I am reporting in this article.

42. Porchownik, J. B.: Ein Fall von multiplem Myelom (Plasmocytom), Virchows Arch. f. path. Anat. **280**:534, 1931.

43. Ghon, A., and Roman, B.: Ueber pseudoleukämische und leukämische Plasma-Zellen-Hyperplasie, Folia haemat. **15**:72, 1913.

scattered plasma cells were found in the right testis, but no gross tumor was seen.[44]

Evidently, then, involvement of the testicles is rare with multiple myeloma, and I believe that the case reported here, in which the testicular lesion was the only extraosseous gross manifestation of the neoplasm, is unique in this respect, unless in the case cited by Porchownik the involvement was similar.

Opinions differ about the origin of extraosseous myeloma. There are four possibilities: (1) direct extension of an intraosseous tumor to adjacent tissues; (2) metastasis; (3) independent (autochthonous) development, parallel with but not secondary to medullary growth;[45] (4) primary extramedullary tumor with or without secondary invasion of the bone marrow.[8b]

Direct extension is not rare. Metastasis also is generally accepted as occurring not infrequently, although Lubarsch [45a] and Hallermann [46] maintained that the apparent metastases are in reality independent parallel developments, and Winkler [47] and Horsch [48] expressed the belief that even the multiple intraosseous tumors were not extensions or metastases but independently originating foci. It is interesting to record here that Borrmann [49] in 1900, when no case of growth outside the bones

44. M. B. Schmidt (Allgemeine Pathologie und pathologische Anatomie der Knochen, Ergebn. d. allg. Path. u. path. Anat. **7**:220, 1900-1901) has been cited by several writers as reporting a case of multiple myeloma with testicular involvement. I have failed to find mention of myelomatous tumor of the testis in his article. It appears that the error was brought about by the fact that Isaac (Die multiplen Myelome, Ergebn. d. Chir. u. Orthop. **14**:325, 1921) in his review referred to three articles by Schmidt, without specifying in which the testicular lesion was noted. The second of the three references was to Schmidt's monograph (Die Verbeitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, Gustav Fischer, 1903) in which he reported the case of a boy of 16 with a testicular tumor, but the diagnosis was lymphosarcoma of the thymus with lymphatic infiltration of the testicles. Nowhere did I find a statement that the condition was multiple myeloma. Apparently authors writing after Isaac had copied the first of his three references without troubling to consult the original for verification.

45. (*a*) Lubarsch, O.: Zur Myelomfrage, Virchows Arch. f. path. Anat. **184**: 213, 1906. (*b*) Pines, L., and Pirogowa, L.: Ueber die multiplen Myelome und das Nervensystem, Arch. f. Psychiat. **84**:332, 1928. (*c*) Zadek, I., and Lichtenstein, H.: Zur Klinik und Zytologie der multiplen Myelome, Folia haemat. **45**: 60, 1931. (*d*) Wallgren.[3]

46. Hallermann, W.: Zur Kenntnis des primären multiplen Myeloms, Deutsches Arch. f. klin. Med. **165**:57, 1929.

47. Winkler, K.: Das Myelom in anatomischer und klinischer Beziehung, Virchows Arch. f. path. Anat. **161**:252, 1900.

48. Horsch, K.: Multiple Myelome und metastatische Knochenmarkstumoren, Beitr. z. klin. Chir. **161**:195, 1935.

49. Borrmann, R.: Myelom, Ergebn. d. allg. Path. u. path. Anat. **7**:852, 1900-1901.

had been reported, predicted that some day metastases to internal organs would be found. He expressed the thought that patients with multiple myeloma usually did not live long enough for metastases to develop and that myeloma cells did not find suitable soil in organs other than the bone marrow.

It is tempting to look on the case presented here as one of primary tumor of the testicle with secondary invasion of the bone marrow, because the testicular tumor had become clinically recognizable when definite roentgen evidence of osseous involvement was still lacking. Jackson, Parker and Bethea [8b] wrote regarding their remarkable case, in which a plasmacytoma of the tonsil preceded medullary involvement by eight years:

> There would seem to be no doubt but that the plasma-cell tumor arose in the tonsil, spread through the lymphatic system, and finally reached the marrow.

In Kreibich's [50] case the first indication of the disease was a wartlike growth on the skin; not until eight weeks later was involvement of the bones demonstrated. Magnus-Levy [17] did not accept this case as one of primary extraosseous involvement, stating the belief—correct, I think—that the growth in the marrow could have existed weeks before it was recognized and that it was probably older than the tumor of the skin. For similar reasons he rejected Krjukoff's [51] and von Werdt's [52] cases. He has insisted that the relative size of the tumors does not determine their chronologic age, because some of them grow more rapidly than others. He stated also, however, what was first suggested by Borrmann,[49] that myelomatous tissue grows poorly outside the bone marrow and that the neoplastic cells find nourishment and favorable growth only in the tissues of their ultimate origin (*ursprünglichen Mutterboden*) or in connection with it, and outside it only in the similar tissue of the lymph nodes.

In my case the tumors in the testes grew more rapidly than would be expected if Magnus-Levy's statement regarding the relative speed of growth of intraosseous and extraosseous lesions were always true, but the fact that the first tumor to be recognized in the testicle (by the patient himself) was relatively large when involvement of the bones could not yet be demonstrated by roentgen examination cannot be accepted, it seems to me, as proof of its primacy. At necropsy the intraosseous growth was found to be diffuse and not in the form of grossly recognizable nodules. Such a diffuse growth could have begun before the

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50. Kreibich, C.: Plasmomyelom der Haut, Folia haemat. **18**:94, 1914.

51. Krjukoff, A.: Le plasmocytome histogène, Folia haemat. (pt. 1) **12**:372, 1911.

52. von Werdt, F.: Zur Kenntnis des Plasmocytoms, Frankfurt. Ztschr. f. Path. **6**:180, 1910-1911.

testicular tumor, or it could have developed simultaneously with it; and, to satisfy Magnus-Levy's dictum, it could have grown and probably did grow more rapidly than the tumor in the testis without being recognizable roentgenologically for a relatively long time because of its diffuseness.

It is of more than academic interest to determine whether a myeloma is single and primary, because treatment of such a circumscribed growth may prevent progression or recurrence of the disease. Thus, Mathias' [53] patient was free from symptoms eighteen months after surgical removal of a localized myeloma of the skull. Bailey [54] irradiated a single myeloma of the humerus, after which the patient, observed six years later, was apparently cured. In Shaw's case of a similar tumor [55] simple curettement was followed by healing and no signs of recurrence a year later. Rogers' [56] patient, with a solitary myeloma of the right femur, was well four years after amputation of the leg.

## NATURE OF MYELOMA CELLS

The nature of the cells involved in the formation of multiple myeloma has been the subject of much study, discussion, speculation and controversy. Wallgren [57] has pointed out that they have been called lymphocytes, lymphoblasts, [58] myelocytes, myeloblasts, plasma cells and erythroblasts.[59] Seemann [60] expressed the belief that in myeloma there may be a hyperplasia of lymphoidocytic (myeloblastic) tissue at first, which later, for as yet unknown reasons, undergoes plasmacytic transformation. Williams [61] advanced the suggestion that "certain biological properties of the osteoblast point to it as a possible cell of origin" of the myeloma cells. Gunn and Mahle [62] reported a case in which they believed

53. Mathias, E.: Zur Myelomfrage, Beitr. z. klin. Chir. **161**:79, 1935.

54. Bailey, C. O.: Plasma Cell Myeloma of the Humerus Treated by Roentgen Radiation, Am. J. Roentgenol. **36**:980, 1936.

55. Shaw, A. F. B.: A Case of Plasma-Cell Myeloma, J. Path. & Bact. **26**: 125, 1923.

56. Rogers, H.: Case of Solitary Plasma-Celled Myeloma, Brit. J. Surg. **17**: 518, 1930.

57. Wallgren, A.: Ueber die Natur der Myelomzellen, Virchows Arch. f. path. Anat. **232**:381, 1921.

58. Klemperer, P.: Ueber das lymphoblastische und das plasmacelluläre Myelom, Beitr. z. path. Anat u. z. allg. Path. **67**:492, 1920.

59. Harbitz, F.: Erythroblastosis and Erythroblastoma, Norsk mag. f. lægevidensk. **84**:211, 1923. Grögler, F.: Zur Kenntnis des Myeloms, Frankfurt. Ztschr. f. Path. **43**:96, 1932.

60. Seemann, G.: Ein Fall von plasma-zellulärem "Myelom," Centralbl. f. allg. Path. u. path. Anat. **48**:212, 1930.

61. Williams, H. W.: Multiple Myeloma of Bone, Am. J. Cancer **16**:540, 1932.

62. Gunn, F. D., and Mahle, A. E.: Megakaryoblastic Myeloma with Crystalline Protein in the Renal Tubules, Tr. Chicago Path. Soc. **15**:23, 1937.

the changes to be megakaryoblastic. Of 643 cases reviewed by Atkinson,[63] the cytologic changes in 332 were not classified, in 207 they were plasmocytic, in 27 myeloblastic, in 24 myelocytic, in 16 lymphocytic, in 5 erythroblastic, in 28 mixed and in 4 of doubtful type. Wallgren [3] expressed the opinion, which seems plausible, that a lymphocytic type does not exist; that newer methods of staining have done away with it, and that all myelomas are made up of cells of the same fundamental type, which may, however, show certain varying stages of development, differentiation or degeneration. Ewing [64] seems to have been in agreement with that when he wrote that multiple myeloma is a "specific malignant tumor of the bone marrow arising probably from a single cell-type." Hirschfeld [65] also expressed doubt about the existence of a lymphocytic type, suggesting that myelocytes may have been mistaken for lymphocytes. Nevertheless, Rosenblum and Kirshbaum [66] in 1936 and Stewart and Weber [36a] in 1938 reported cases of what they called lymphocytic myeloma and Dameshek [67] included multiple myeloma in the group of tumors arising from lymphoid tissue. This is contrary to the classification by the Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists,[68] in which myelomas are grouped with the myeloid tumors, and the term multiple myeloma is used as a synonym of multiple aleukemic myelocytoma.

In a large proportion of the cases the component cells, with their deeply basophilic cytoplasm and often eccentrically placed nuclei, resemble plasma cells more closely than any other known form of cell; hence the designations plasmacytoma, plasmoma, multiple myeloma of the plasma cell type and plasmacytic leukemia [69] have been applied. Often, however, the cells lack certain characteristics of typical plasma cells. The nucleus frequently does not have the coarse radial arrangement of the chromatin; the perinuclear *Hof* is often absent, and the characteristic staining reaction of plasma cells may be lacking. In view of their uncertain identity, Wallgren [3] suggested that they be spoken of merely

63. Atkinson, F. R. B.: Multiple Myelomata, M. Press **195**:312 and 327, 1937.

64. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

65. Hirschfeld, H.: Ueber die multiplen Myelome, Folia haemat. **9**:1, 1910.

66. Rosenblum, A. H., and Kirshbaum, J. D.: Multiple Myelomas with Tumor-Like Amyloidosis: Clinical and Pathologic Study, J. A. M. A. **106**:988 (March 21) 1936.

67. Dameshek, W.: Progress in Hematology in 1936, New England J. Med. **218**:15, 1938.

68. Callender, G. R.: Tumors and Tumor-like Conditions of the Lymphocyte, the Myelocyte, the Erythrocyte and the Reticulum Cell, Am. J. Path. **10**:443, 1934.

69. (*a*) Piney, A.: Plasma Cell Leukemia, Folia haemat. **30**:173, 1924. (*b*) Osgood, E. E., and Hunter, W. C.: Plasma Cell Leukemia, ibid. **52**:369, 1934. (*c*) Gluzinski, A., and Reichenstein, M.: Myeloma und Leucaemia lymphatica plasmacellularis, Wien. klin. Wchnschr. **19**:336, 1906.

as myeloma cells. Zadek and Lichtenstein,[45c] Hallay and Odor [70] and others [71] expressed the same opinion. According to Zadek and Lichtenstein, the cells that form myeloma are not normal bone marrow cells—that is, they are neither typical myeloblasts, nor lymphoblasts nor characteristic plasma cells. The cells are abnormally differentiated (*entdifferenzierte*) cells derived from the bone marrow, which in accordance with Wallgren's suggestion, are to be designated myeloma cells.

Transitional types between myeloblasts and plasma cells were seen in the case reported here, as in the cases of Cappell [72] and others.[73] Christian [73a] wrote:

> It seems possible to arrange the cells of these tumors in series so that between the cells of succeeding cases the differences are slight, though the differences between the cells at the extremes are fairly great.

That "myeloma cells" are related to myeloid cells is indicated by the fact that Forman and Warren [74] and Beck and McCleary [75] reported cases in which the peroxidase reaction was positive. In others, however, as, for example, Morse's [76] 3 cases and Burnett and Johnson's [77] case, the reaction was negative. Since the test is not reliable for very young cells, a negative reaction is without differential diagnostic value.

Zadek [78] and others [79] offered the opinion, based on studies of marrow obtained by sternal puncture, that plasma cells are derived, even normally, from the reticuloendothelial stroma of the bone marrow, and that myeloma cells have the same origin.

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70. Hallay, I., and Odor, B.: Ueber einen Fall von multiplem Myelom, Ztschr. f. klin. Med. **120**:32, 1932.

71. (*a*) Markoff, N.: Die Beurteilung des Knochenmarks durch Sternalpunktion, Deutsches Arch. f. klin. Med. **179**:113, 1936. (*b*) Curtze, W.: Untersuchungen über multiple Myelome, Folia haemat. **60**:1, 1938. (*c*) Heilmann, P.: Beitrag zur Myelomfrage, Centralbl. f. allg. Path. u. path. Anat. **58**:405, 1933.

72. Cappell, D. F.: Two Cases of Myelomatosis: (1) Diffuse Plasma-Celled; (2) with Tumour-like Nodules and Visceral Lesions, J. Path. & Bact. **32**:293, 1929.

73. (*a*) Christian, H. A.: Multiple Myeloma: A Histological Comparison of Six Cases, J. Exper. Med. **9**:325, 1907. (*b*) Krjukoff.[81]

74. Forman, J., and Warren, J. H.: The Identification of the Cells in Myelomas by Means of the Indol-Phenol Blue Synthesis, J. Cancer Research **2**: 79, 1917.

75. Beck, H. G., and McCleary, S.: Multiple Myeloma with Bone Marrow Plasma Cells in the Blood, J. A. M. A. **72**:480 (Feb. 15) 1919.

76. Morse, P. F.: The Peroxidase Reaction in Three Cases of Multiple Myeloma of the Bones with Remarks Concerning the Nosological Position of the Tumors, J. Cancer Research **5**:345, 1920.

77. Burnett, C. T., and Johnson, W. C.: Mulitple Myeloma, Colorado Med. **27**:178, 1930.

78. Zadek, I.: Die hämatologische Diagnose des multiplen Myeloms, Wien. klin. Wchnschr. **51**:632, 1938.

79. Rohr, K.: Blut- und Knochenmarksmorphologie der Agranulocytosen, Folia haemat. **55**:305, 1936. Curtze.[71b]

Support for the contention that only one type of cell is involved in all cases of multiple myeloma is found in the fact, which has been pointed out by others,[80] that in recent years the number of reports of plasmacytoma, compared with other types, has increased. Thus, Wallgren [57] found that of the 25 cases reported between 1900 and 1904, in only 3 was a diagnosis of plasmacytoma made, whereas in half of the 30 cases between 1905 and 1909 and 15 of the 25 between 1910 and 1914 that designation was given. Fleischhacker and Klima [81] found that all but 1 of their 10 cases were instances of plasmacytoma, and the diagnosis in the exceptional case was not verified by necropsy.

The case reported here illustrates the difficulties that may be met. The testicular tumors and the bone marrow contained many so-called atypical plasma cells, and other cells, found also in the kidneys and spleen, appeared to be myelocytes and myeloblasts. However, I am convinced that all of them were variations of the same basic type. This is in accord with the views of Smith and Silberberg,[82] who wrote regarding their case that the "multiple myeloma of the hemoblastic type . . . consisted of a large variety of blood cells in various stages of differentiation" and stated:

> It is only logical to assume that all the different cell types may have a common source. This progenitor cell, proliferating under tumor conditions, retains all its hematopoietic potentialities so that differentiation may take place in all directions and a most varied cytologic structure result.

Patek and Castle [27g] stressed "the desirability of regarding this plasma cell tumor (plasmacytoma) as a pathologic entity whose different forms are not distinct diseases, but are simply gradations in extent and activity of the same disease process." From a histologic standpoint, therefore, multiple myeloma may be regarded as an entity. This does not mean that attempts to recognize subgroups or variations (erythroblastic, myeloblastic and plasmacytic) should be abandoned. I agree with Pentman [80] that there are differences in type but not necessarily in origin.

### RELATION OF MYELOMA TO LEUKEMIA

The diffuse nature of the medullary growth in this and other reported cases [83] strengthens the belief that multiple myeloma is related to the

80. Pentman, I.: Beitrag zu den multiplen Myelomen, Virchows Arch. f. path. Anat. **258**:161, 1925. Mathias.[58] Seemann.[60]

81. Fleischhacker, H., and Klima, R.: Beitrag zur Kenntnis des multiplen Myeloms, der plasmacellulären Leukämie und des plasmacellulären Granuloms, Folia haemat. **56**:5, 1936.

82. Smith, R. P., and Silberberg, M.: Multiple Myeloma of Hemocytoblastic Type, Arch. Path. **21**:578 (May) 1936.

83. Jochmann, G., and Schumm, O.: Zur Kenntnis des Myeloms und der sogenannten Kahler'schen Krankheit, Ztschr. f. klin. Med. **46**:445, 1902. Abrikosoff, A., and Wulff, F.: Ueber Eiweisskrystallbildung in einem Fall von Myelom, Verhandl. d. deutsch. path. Gesellsch. **22**:270, 1927.

leukemias. The testicular tumors in the present case were not circumscribed but resembled the extramedullary nodular infiltrations found in the internal organs in some cases of leukemia (fig. 2). Foord and Randall [7b] found a leukemia-like growth of plasma cells in the spleen, lymph nodes, liver and adrenal glands. Seemann [60] has pointed out the similarity between myeloma and chloroma. Battaglia,[84] Piney and Riach [85] and Osgood and Hunter [69b] called attention to the morphologic gradations in the development of myelomatous tissue, from solitary or scattered circumscribed nodules to diffuse hyperplasia, the latter closely resembling leukemia. According to Hamman,[86] multiple myeloma "belongs to that remarkable group of diseases that stand midway between the leukemias and the malignant tumors."

In several reported cases [87] the "myeloma cells" have been observed in the circulating blood, in 1 case making up as much as 70 per cent of the leukocytes.[69c] In my case the greatest concentration found at any time was 10 per cent (fig. 4). In addition, there were some unclassified cells, some or all of which probably belonged to the same category. Osgood and Hunter [69b] expressed the belief that their patient, with 54 per cent "plasma cells" in the blood, had plasmacytic leukemia rather than multiple myeloma. I doubt that such a differentiation was warranted. It is more likely that the difference was merely one of diffusion or of circumscription of the same fundamental pathologic process.

Vance [88] in 1916 wrote that in "no case have myelocytes been found in the circulating blood." That is no longer true. Several writers have since then reported the presence not only of myelocytes but of myeloblasts in the peripheral blood. In the case presented here they were present almost constantly (fig. 4), making up from 2 to 19 per cent of the leukocytes. It was because of this that the differentiation from myeloid leukemia was not established until histologic study of the testicular tumor and necropsy material had been made. Such a differ-

84. Battaglia, F.: Beitrag zur Kenntnis der Systemerkrankungen des Knochenmarks (Myelom und aleukämische Myelose), Virchows Arch. f. path. Anat. **267:** 106, 1928.

85. Piney, A., and Riach, J. S.: Multiple Myeloma: Aleukemic and Leukemic, Folia haemat. **46:**37, 1931.

86. Hamman, L., in discussion on Scott, J. W.: Multiple Myeloma, South. M. J. **17:**478, 1924.

87. Muller, G. L., and McNaughton, E.: Multiple Myeloma (Plasmacytomata) with Blood Picture of Plasma Cell Leukemia: Report of Two Cases, Folia haemat. **46:**17, 1931. Jores, A., and Bruns, W.: Ein Fall von "malignem Plasmom" mit einem Beitrag zur sogenannten "Plasmazellenleukämie," ibid. **55:***227*, 1936. Ghon and Roman.[43] Footnote 69 *b* and *c*. Fleischhacker and Klima.[81] Piney and Riach.[85]

88. Vance, B. M.: A Case of Multiple Myelomata, with a Discussion of Its Nature and Origin, Am. J. M. Sc. **152:**693, 1916.

entiation may be difficult and, perhaps, not always warranted. Strong supporting evidence of the similarity and close relation of these diseases is supplied by Furth's [89] experiments with mice, in which, after injection of a transmissible strain of myeloid leukemia, leukemia developed in some animals and myeloma in others. Among the differences between the two conditions, Battaglia [84] mentioned the greater tendency of leukemia to infiltrate extraosseous tissues and of myeloma to destroy bone and to form nodules. Despite these differences the evidence is against Deelman's [90] terse dictum: "Myeloma is a tumor; leukemia is not a tumor."

The following suggested classification of myelomas emphasizes the transition and relation between various types, bordering at one extreme on the definite neoplastic tumors and at the other on leukemia:

1. Solitary benign tumor in or out of the bone marrow, which may be amenable to surgical removal or irradiation with hope of cure.

2. Single or multiple malignant tumor of the bones, with or without extraosseous growth.

3. Diffuse myelomatosis of the bone marrow, with or without infiltration of other organs.

4. "Plasmacytic" leukemia.

This schema is in agreement with the idea Waugh [91] expressed about the "interrelation of various systemic hematopoietic processes," according to which they "form a quite definite series which blends from one into the other." Schmidt [92] wrote as long ago as 1900 that a close relation existed between myeloma and pseudoleukemia on the one hand and sarcoma on the other, and that with these as well as with lymphoma and lymphosarcoma it is not easy to draw the line between hyperplasia and true tumor.

Certain experimental studies lend strong support to the conception of unitarian origin of the various forms of myeloma and of its intermediate position between frank tumor and diffuse hyperplasia. Fischer-Wasels [93] produced a variety of lesions, including lymphosarcoma and myeloid leukemia, in mice subjected to mild but prolonged poisoning with indole. More recently Furth,[94] experimenting with the transmis-

89. Furth, J.: Transmission of Myeloid Leukemia in Mice: Its Relation to Myeloma, J. Exper. Med. **61**:423, 1935.

90. Deelman, H. T.: Myeloma in Relation to Leukemia, Nederl. tijdschr. v. geneesk. **80**:118, 1936.

91. Waugh, T. R.: The Interrelation of Various Systemic Hematopoietic Processes, Am. J. M. Sc. **193**:337, 1937.

92. Schmidt, cited in footnote 44.

93. Fischer-Wasels, B.: Experimentelle Grundlagen und Folgerungen der Regenerationstheorie der Geschwulstbildung, Klin. Wchnschr. **11**:1977, 1932.

94. Furth, J.: Transmission of Myeloid Leukemia in Mice, Proc Soc. Exper. Biol. & Med. **31**:923, 1934.

sion of myeloid leukemia in mice, found that he could produce localized tumors or extensive, more or less diffuse infiltration of several organs and the presence of leukemic cells in the circulating blood, depending on whether the injections were made subcutaneously or intravenously. These results were confirmed by Kaalund-Jørgensen.[95] Furth, Seibold and Rathbone [96] obtained similar results with lymphomatosis of mice. More important still in this connection are the previously cited additional experiments of Furth,[89] in which intravenous injection of a transmissible strain of myeloid leukemia in mice resulted in the development of diffuse myelosis in some of the animals and of multiple myeloma in others.

## SUMMARY AND CONCLUSIONS

A case of multiple myeloma is reported in which there were certain noteworthy features, including tumors in the testes, absence of pain, absence of definite roentgen evidence of the disease in the bones, presence of myeloma cells in the circulating blood and hyperproteinemia without Bence Jones proteinuria. As a result of a study of this case and a review of the literature, certain conclusions may be drawn:

1. Multiple myeloma is a neoplastic disease occupying a position midway between frank tumors and diffuse (leukemic) hyperplasia. The growths are composed of cells of myeloid origin, which usually resemble plasma cells and which may differentiate in varying directions to form apparently distinct types of the disease.

2. The usual site of origin is the bone marrow but extramedullary origin may occur.

3. The outstanding symptoms are pain and weakness, but pain may not develop until injury to a diseased bone occurs; it is usually absent in extraosseous lesions and may not be present when the process in the bone marrow is diffuse. Multiple myeloma should be thought of as a possible cause of unexplained pain in various parts of the body, especially backache.

4. Renal disease is a common complication of multiple myeloma. In some cases it appears to be a form of hydronephrosis secondary to tubular obstruction by casts of Bence Jones protein; in others the mechanism of its production is not known.

5. Treatment in the majority of cases is wholly symptomatic; exposure to roentgen rays may be effective in relieving pain. The prognosis is hopeless, except in the occasional cases of solitary tumor, in which surgical removal or roentgen therapy may result in cure.

95. Kaalund-Jørgensen, O.: Eine überimpfbare Myelomatose der Maus, Ztschr. f. Krebsforsch. **42**:393, 1935.

96. Furth, J.; Seibold, H. R., and Rathbone, R. R.: Experimental Studies on Lymphomatosis of Mice, Am. J. Cancer **19**:521, 1933.

6. Examination by means of roentgen rays is one of the most important diagnostic procedures, although the radiologist may be unable to differentiate between myeloma and metastatic carcinoma.[97] Other methods of examination may be of equal or even greater value. They may confirm a suspicion of myeloma, or they may suggest the diagnosis when it had not been thought of before. They include:

(*a*) Biopsy of an involved portion of bone. It establishes the diagnosis with reasonable certainty if it shows the presence of typical myeloma cells.

(*b*) Sternal puncture. It may reveal the characteristic cells, even when the sternum is not grossly affected.

(*c*) Hyperproteinemia. A serum protein level of more than 10 per cent is unusual with other diseases.

(*d*) Hypercalcemia, with a normal or high serum phosphorus level. This combination distinguishes multiple myeloma from hyperparathyroidism.

(*e*) Bence Jones proteinuria. Although absent in many cases and present occasionally with other diseases, it is strong presumptive evidence of multiple myeloma.

(*f*) The presence of myeloma cells ("atypical plasma cells") in the circulating blood. They are usually absent, but may be present in large numbers and may then be the first definite sign pointing to the correct diagnosis.

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97. Holmes, G. W., in discussion on Multiple Myeloma, Cabot Case 23122, New England J. Med. **216**:521, 1937.

# LIPOCAIC AND FATTY INFILTRATION OF THE LIVER IN PANCREATIC DIABETES

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In 1924 Fisher [1] and Allan, Bowie, Macleod and Robinson [2] reported that completely depancreatized dogs adequately treated with insulin usually failed to survive more than two to three months. At autopsy the most prominent change observed was an extensive fatty infiltratration and degeneration in the liver. In general these findings have been widely confirmed. Occasional animals have been observed in which the fatty changes developed and death occurred in five to six weeks, while others have survived for six months to a year and still others have failed to show any evidence of disease of the liver and have survived for long periods with no supplementary treatment other than the insulin therapy. The latter constitute a small minority and will be discussed later. The addition of raw pancreas to the diet of the depancreatized dog was found by Allan, Bowie, Macleod and Robinson to prevent or relieve the fatty changes in the liver and to permit the animal to survive indefinitely when treated also with insulin. In 1936 Dragstedt, Van Prohaska and Harms [3] reported that the beneficial effect of feeding pancreas in this connection could not be accounted

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1. Fisher, N. F.: Am. J. Physiol. **67**:634, 1924.

2. Allan, F. N.; Bowie, J. J.; Macleod, J. J. R., and Robinson, W. L.: Brit. J. Exper. Path. **5**:75, 1924.

3. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Am. J. Physiol. **117**:175, 1936.

for on the basis of its content of pancreatic enzymes or of choline but was due to a specific substance, believed to be a new hormone. The name lipocaic was suggested for this substance. It is the purpose of the present report to present further evidence which indicates that lipocaic is an internal secretion of the pancreas.

## FATTY CHANGES IN THE LIVER IN DIABETES MELLITUS AND IN PANCREATIC DIABETES

The occurrence of fatty changes in the liver in diabetes mellitus has apparently long been known and was described from time to time in the older literature. More recently (1931) Meyer [4] reported that hepatic dysfunction was frequent in diabetes mellitus and that in 28 per cent of the series of cases studied by him there was either laboratory or clinical and laboratory evidence of impairment of the liver. In contrast to other observers, he concluded that the older the patient and the longer the diabetes mellitus remained uncontrolled, the more frequently hepatic dysfunction became demonstrable. White [5] (1932) remarked that fatty infiltration of the liver in diabetic children was common and presented roentgen evidence of decrease in its size after administration of insulin and dietetic management. Hanssen [6] (1936) found marked enlargement of the liver in 12 of a series of 44 diabetic patients under 20 years of age. Here also the enlargement receded under better control of the diabetes by the use of protamine zinc insulin and a diet relatively low in carbohydrate.

Von Mehring and Minkowski [7] (1890) called attention to the accumulation of fat in the liver in depancreatized dogs that died of diabetes, and a vivid picture of this condition was given by Naunyn [8] (1906), who likened the microscopic appearance to that of the liver in the most severe type of phosphorus poisoning. These observations were confirmed by many workers in the period before the isolation of insulin, and we have seen the manifestation many times.

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4. Meyer, E. L.: Function of the Liver in Diabetes Mellitus, Arch. Int. Med. **47**:182 (Feb.) 1931.

5. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, p. 169.

6. Hanssen, P.: Enlargement of the Liver in Diabetes Mellitus, J. A. M. A. **106**:914 (March 14) 1936.

7. von Mehring, J., and Minkowski, O.: Arch. f. exper. Path. u. Pharmakol. **26**:371, 1890.

8. Naunyn, B.: Der Diabetes mellitus, ed. 2, Vienna, Alfred Hölder, 1906, p. 118.

### FATTY INFILTRATION OF THE LIVER IN DEPANCREATIZED DOGS DUE TO POOR CONTROL OF THE DIABETES BY INSUFFICIENT AMOUNTS OF INSULIN AND FATTY CHANGES IN THE LIVER DUE TO LIPOCAIC DEFICIENCY

The recognition of the occurrence of fatty infiltration of the liver both in diabetes mellitus and in pancreatic diabetes due to inadequate administration of insulin raised the question as to the relation of this type of fatty liver to that due to lipocaic deficiency. The following experiments were done to give some information on this problem:

Complete pancreatectomy was performed on 2 dogs and a diet of bread, meat and milk provided, but no insulin given. At the time of operation the livers were observed to be normal in size and color, and microscopic examination of biopsy specimens showed the usual minimum amount of fat. One animal was killed after forty-eight hours and the other after seventy-two hours. A marked fatty infiltration in the liver (graded 4 plus) was found in each case. Pancreatectomy was then performed on 3 additional animals. In each case the liver was observed to be of normal color and size at operation, and sections stained for fat showed no fat or a few fine granules. The diet was again bread, meat and milk, and no insulin was administered. After twenty-four hours a biopsy was made of the liver of 1 animal and a definite fatty infiltration (graded 2 plus) was found. After the biopsy this animal was placed on protamine zinc insulin therapy and the diabetes well controlled. After nineteen days of such treatment a second biopsy was made, and at this time the liver was found to be normal. The diet and insulin treatment were then continued as before for sixty-six days. The animal then began to show evidence of lipocaic deficiency (decreased excretion of dextrose, increased sensitivity to insulin and decreased activity), and a third biopsy of the liver disclosed a return of fat in the liver, more marked than before (graded 3 plus). The course of events for the other 2 depancreatized dogs was similar. Both showed marked fatty infiltration of the liver (graded 4 plus) in twenty-four and in ninety-six hours when given no insulin. Good control of the diabetes with protamine zinc insulin produced a complete removal of fat from the liver in 1 animal in nine days and a marked reduction in the other in four weeks. In each case the insulin treatment was continued, but in spite of this a reaccumulation of fat occurred in the liver in forty-five and in ninety-three days in these 2 animals. Both showed the usual signs of lipocaic deficiency, and both responded to the oral administration of lipocaic by increased excretion of dextrose, increased insulin tolerance and removal of fat from the liver.

Numerous other observations have been made which confirm the findings in the experiments just described. These may be summarized

in the following general statement: An immediate and marked accumulation of fat occurs in the liver cells of dogs within the first two or three days after complete pancreatectomy. This is particularly striking in well nourished or fat animals and when no insulin or relatively small doses are given and a large excretion of dextrose occurs. Such animals often exhibit marked lipemia (total lipids reaching 2 to 3 per cent), and severe acidosis may occur. These abnormalities are probably to be attributed to poor control of the diabetes with insufficient amounts of insulin. They are promptly corrected when insulin is administered in a more adequate amount and manner. However, when this is done and treatment of the diabetes is carried out most carefully, there occurs a steadily lessening excretion of dextrose in spite of continually decreasing doses of insulin, until after six to eight weeks the animal may excrete only a gram or 2 per day and receive only 2 to 3 units of insulin. Larger amounts of insulin, even 5 units, may at this time provoke fatal hypoglycemic convulsions. Superficially it might appear as though the animal were recovering from the diabetes. However, progressive weakness and loss of appetite develop; the animal becomes emaciated, and death occurs. At autopsy the liver is found to be enlarged to three or four times its normal size and so infiltrated with fat that the normal structure is entirely obscured.

These findings suggest that two entirely distinct types of fatty liver develop in depancreatized dogs, one due to insulin deficiency and one due to lipocaic deficiency. As will be described in detail elsewhere, there appear to be definite histologic differences between the two types. In the type that appears early in depancreatized dogs treated inadequately with insulin, the normal lobular architecture is preserved and the fat is usually present in the liver cells in the form of fine granules or small droplets. In the type that appears later (in six to eight weeks as a rule), the structure of the liver is usually destroyed and large droplets of fat occupy the place of the liver cells. Evidence of impaired hepatic function, as revealed by the bromsulphalein test, is almost always present, whereas it is less common with fatty liver of insulin deficiency. The most significant difference between the two types, however, lies in the response to insulin. The animal with fatty liver due to poor control of the diabetes tolerates large doses of insulin well, and such treatment clears the liver of fat and reduces the hyperlipemia when this is present. The animal with fatty liver due to lipocaic deficiency displays commonly hypolipemia, and hypoglycemic convulsions develop with small doses of insulin. Furthermore, when such animals succumb to the insulin they still have the excessively fatty liver.

Evidence suggesting the occurrence of these two types of fatty infiltration of the liver in human diabetes mellitus has recently appeared.

Grayzel and Radwin [9] (1938) treated 3 young diabetic patients with hepatomegaly by means of lipocaic and secured a striking recession of the liver to its normal size. When the lipocaic was discontinued, the hepatomegaly returned, and it again receded when lipocaic therapy was resumed. The diabetes in these patients had been well controlled by diet and insulin therapy. Rosenberg [10] (1938) reported a case in which marked hepatomegaly and impaired hepatic function in an adult with mild diabetes did not improve with better control of the diabetes by diet and insulin therapy. A biopsy specimen of the liver secured at operation revealed a marked fatty infiltration similar to that seen in the depancreatized dog. The administration of lipocaic brought about improvement in hepatic function, recession in the size of the liver and disappearance of the fat, as revealed by a second biopsy. Marble, White, Bogan and Smith [11] (1938) studied 60 cases of pronounced hepatomegaly among 1,077 diabetic children in Joslin's clinic and came to the conclusion that the manifestation resulted from fatty infiltration and was usually due to poor control of the diabetes. The oral administration of raw pancreas in 2 cases and of betaine hydrochloride in 12 produced little or no improvement, while better control of the diabetes by the use of protamine insulin did result in decrease in the hepatomegaly. It is noteworthy that the patients displayed no impairment of hepatic function and were not unusually sensitive to insulin, as is true of persons with fatty liver of lipocaic deficiency.

### SURVIVAL OF COMPLETELY DEPANCREATIZED DOGS TREATED WITH INSULIN WITHOUT THE ADDITION OF LIPOCAIC, CHOLINE OR LECITHIN IN THE DIET

The conclusion independently arrived at by Fisher [1] (1924) and by Allan, Bowie, Macleod and Robinson [2] (1924) that the completely depancreatized dog would not survive more than a few months even though adequately treated with insulin was supported by the subsequent studies of Best and his associates.[12] The data presented in a previous report

9. Grayzel, H. G., and Radwin, L. S.: Hepatomegaly in Juvenile Diabetes Mellitus Treated with Pancreatic Extract, Am. J. Dis. Child. **56**:22 (July) 1938.

10. Rosenberg, D. H.: Am. J. Digest. Dis. **5**:607, 1938.

11. Marble, A.; White, P.; Bogan, I. K., and Smith, R. M.: Enlargement of the Liver in Diabetic Children, Arch. Int. Med. **62**:740 (Nov.) 1938. White, P.; Marble, A.; Bogan, I. K., and Smith, R. M.: ibid. **62**:751 (Nov.) 1938.

12. (*a*) Best, C. H.; Channon, H. J., and Ridout, J. H.: J. Physiol. **81**:409, 1934. (*b*) Best, C. H.; Ferguson, G. C., and Hershey, J. M.: ibid. **79**:94, 1933. (*c*) Best, C. H., and Hershey, J. M.: ibid. **75**:49, 1932. (*d*) Best, C. H.; Hershey, J. M., and Huntsman, M. E.: ibid. **75**:56, 1932. (*e*) Best, C. H., and Huntsman, M. E.: ibid. **75**:405, 1932. (*f*) Best, C. H., and Ridout, J. H.: ibid. **78**:415, 1933.

from this laboratory [13] were in harmony with this view. Eight depancreatized dogs treated with insulin and given a diet of meat, bread and milk and large amounts of pancreatic juice survived only twenty-four, forty-one, forty-five, fifty-six, sixty-five, sixty-eight, seventy-five and one hundred and forty-two days. All these animals were found to have extensive fatty infiltration of the liver at autopsy. We now have data on 154 depancreatized animals. In 92 per cent of the total number fatty changes in the liver were revealed by laparotomy and biopsy. In 4 of a later group insulin therapy and a diet of bread, whole milk and meat with the daily addition of cod liver oil and brewers' yeast but without lipocaic or choline supplements were continued. All died, in twenty-six, thirty-one, seventy-five and one hundred and fifty-five days, and at autopsy the liver in each case contained over 30 per cent fat by chemical analysis. In 13 of the 154 the liver remained normal on repeated examination. These animals were not given lipocaic or choline but were continued in the laboratory on various different diets. All eventually died, after intervals varying between two and seventeen months. It is thus evident that in a small proportion of insulin-treated depancreatized dogs (about 8 per cent in our series) the characteristic fatty changes in the liver do not develop. The reason for this is obscure. It is probably not due to the presence of accessory pancreatic tissue, since with a little experience it is not difficult for an observer to be sure that all pancreatic tissue is removed at operation, and the intramural portions of the pancreatic ducts have always been excised. In a recent paper Chaikoff and Kaplan [14] (1937) reported that "When maintained with insulin and a high-calorie, high-protein, high-vitamin diet, completely depancreatized dogs may survive for as long as 4 to 5 years," and that "This length of survival makes it unnecessary to assume that raw pancreas or extracts thereof or choline supplements (i. e., in addition to that contained in the dietary constituents) are essential for the survival of the completely depancreatized dog receiving insulin." It is possible that the discrepancy between the conclusions of these workers and those we have made from our own data may be accounted for in part by the following quotation from their paper: "In order to avoid chronic undernutrition, animals that failed to regain a good appetite within a month or so after pancreatectomy were discarded." It has been our experience that insulin-treated depancreatized dogs suffering from lipocaic deficiency usually display, among other symptoms, a loss of appetite and decreased activity. This is regularly associated with a

13. Van Prohaska, J.; Dragstedt, L. R., and Harms, H. P.: Am. J. Physiol. **117**:166, 1936.

14. Chaikoff, I. L., and Kaplan, A.: J. Nutrition **14**:459, 1937.

fatty liver and is promptly relieved by administration of lipocaic. For this reason among others it does not seem wise to us to discard part of the data in attempting to decide the usual course of the insulin-treated depancreatized dog.

As noted before, 92 per cent of 154 insulin-treated depancreatized dogs in our series showed fatty changes in the liver which could be attributed to lipocaic deficiency. Twelve of these, including the 8 animals reported on in a previous paper,[13] were given no effective supplementary treatment, and all died within a few months. The great majority of the animals with fatty liver were given supplementary treatment with raw pancreas, various pancreas fractions, choline or betaine hydrochloride. In spite of this, a good many valuable data bearing on this question of survival have accumulated which because of limitations of space cannot be presented in detail. In many instances depancreatized animals with fatty liver displaying the other symptoms of lipocaic deficiency (decreased activity, loss of appetite, decreased excretion of dextrose and decreased insulin tolerance) have been restored to normal by the administration of an effective pancreas preparation and maintained so for several months, only to experience prompt development of fatty liver again and die when the lipocaic was discontinued.

### CRITERIA OF LIPOCAIC DEFICIENCY

The symptoms and signs of lipocaic deficiency were described in large part in a previous paper [13] and have been alluded to in the foregoing section. An erroneous impression has arisen somehow that the sole criterion of lipocaic deficiency employed in this laboratory has been the demonstration by histologic means of fat in a small section of liver taken by biopsy (Chaikoff and Kaplan;[14] Aylward and Holt;[15] Ivy and Crandall [16]). Indeed, Aylward and Holt stated:

> It may not be out of place, however, to point out that Dragstedt and his collaborators rested their case entirely upon histological evidence, which does not invariably give an accurate picture of the chemical state of the liver.

Because of this confusion, we should like to repeat here the criteria that have been employed both for the demonstration of lipocaic and for determining the activity of a pancreas extract under study.

In the final analysis the demonstration of lipocaic depends on the recognition that the depancreatized dog fed a mixed diet of protein, carbohydrate and fat is not restored to a normal state by the adequate

15. Aylward, F. X., and Holt, L. E.: J. Biol. Chem. **121**:61, 1937.

16. Ivy, A. C., and Crandall, L. A., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1938, vol. 7, p. 404.

administration of insulin and the external pancreatic secretion. The oral administration of pancreas or of a fat-free alcoholic extract of pancreas corrects the remaining deficiency, prevents the accumulation of abnormal amounts of fat in the liver and makes survival for a long period in a good nutritional state possible. In the assay of pancreas fractions for lipocaic, several animals, usually 3, were depancreatized and placed on a standard diet, and careful measurement was made of the amount of dextrose excreted daily and the insulin requirement. Commonly 20 to 30 units of regular insulin daily were required to keep the dextrose excretion under 10 Gm., although wide variations were found in different animals. A progressive decrease in dextrose excretion and a consequent decrease in insulin requirement were found to occur, so that after four to six weeks the animals might excrete less than 5 Gm. of dextrose daily and receive only 2 to 5 units of insulin and even on these small doses display severe and even fatal hypoglycemic convulsions. Symptoms such as decreased activity, loss of appetite, apathy and some muscular weakness were usually apparent. A laparotomy was then done and the liver inspected. A marked fatty infiltration of the liver is unmistakable even on gross inspection, and moderate degrees of fatty change are readily appreciated. The liver is enlarged, bright yellow and friable. A biopsy specimen may be secured with little or no bleeding. Usually the fat appeared to be uniformly distributed through the liver, and a representative section was always chosen for the biopsy. In our first experiments histologic examination only was made of the biopsy specimen, but during the past two years this has been supplemented by chemical determination of the total lipid content. After the laparotomy and biopsy the animals were fed the test pancreas fraction and the material was concluded to contain an effective dose of lipocaic if the animals displayed clinical improvement (increase in weight, increase in appetite and increased activity), an increase in dextrose excretion (occasionally to as much as 20 to 60 Gm. per day) and an increase in insulin requirement and tolerance (a return to the amount of insulin required immediately after pancreatectomy). This conclusion was always verified by a second laparotomy, inspection of the liver and biopsy. Since the previous report we have made use of two additional criteria, namely the bromsulphalein test of hepatic function (Goodpasture, Vermeulen, Donovan and Dragstedt [17]) and measurement of the concentration of the total blood lipids. In the presence of a fatty liver due to lipocaic deficiency the hepatic function is impaired, as indicated by abnormal retention of bromsulphalein, and the concentration of total lipids in the blood is reduced to about

17. Goodpasture, W. C.; Vermeulen, C.; Donovan, P. B., and Dragstedt, L. R.: Am. J. Physiol. **124**:642, 1938.

half the normal concentration. Both are returned to normal, usually within two weeks, by the oral administration of an adequate dose of lipocaic.

Criticism directed to our use of laparotomy, inspection and biopsy of the liver in these studies seems to us unwarranted. The most obvious defect in the depancreatized insulin-treated dog is the extreme fatty change in the liver. We are interested in determining the therapeutic effectiveness of various pancreatic extracts in this condition. It seems obvious, then, that the presence of fatty liver should be verified before the test is made, particularly since, as we have indicated, not all depancreatized dogs show it. It is true that determination of the amount of fatty infiltration in the liver by inspection and microscopic examination

TABLE 1.—*Correlation Between the Estimation of Fat in the Liver by Histologic and by Chemical Methods*

| No Fat* | | Fat + | | Fat ++ | | Fat +++ | | Fat ++++ | |
|---|---|---|---|---|---|---|---|---|---|
| Animal No. | Fat, % | Animal No. | Fat, % | Animal No. | Fat, % | Animal No. | Fat, % | Animal No | Fat, % |
| 711 | 4.7 | 330 | 6.3 | 711 | 12.8 | 654 | 43.7 | 665 | 39 5 |
| 314 | 4 3 | 651 | 7.6 | 711 | 7.8 | 678 | 13.1 | 888 | 39.3 |
| 514 | 13.4 | 976 | 6.0 | 711 | 10.0 | 674 | 12.9 | 665 | 36.1 |
| 514 | 4.4 | 654 | 6.8 | 654 | 20.5 | 896 | 21.0 | 695 | 35.2 |
| 653 | 6.6 | 885 | 6.8 | 940 | 12.5 | 768 | 28.2 | 673 | 42.0 |
| 784 | 4.0 | 884 | 8.2 | 678 | 12.1 | 847 | 35.2 | 715 | 38.8 |
| 801 | 4.0 | 330 | 21.3 | 678 | 9.1 | 979 | 32.0 | 717 | 36.8 |
| 955 | 6.8 | 955 | 14.0 | 653 | 14.4 | 969 | 30.4 | 726 | 45.0 |
| 883 | 7.8 | 96 | 7.0 | 883 | 15.0 | 940 | 23.0 | 330 | 38.4 |
| 651 | 5.5 | 883 | 11.2 | 717 | 23.8 | 967 | 17.6 | 940 | 33.0 |
| Average | 6.15 | | 9.54 | | 13.8 | | 24.71 | | 38.41 |

* The normal liver contains considerable fat which is not visible in stained sections.

is not always accurate, especially when only slight changes exist, but then, of course, no conclusions can be drawn. Estimation of the degree of fatty infiltration in the liver by histologic methods is, however, more accurate than some physicians may have supposed. This is evident from inspection of table 1, in which are included data from biopsy of 50 livers in which independent histologic examination and chemical determination of fat content were made by two different observers. Sections were stained with scarlet red and the amount of fat present indicated by grades from zero to 4 plus. For the chemical determination of fat a portion of the fresh biopsy specimen was repeatedly extracted with alcohol and ether with the aid of a reflux condenser after being ground with sand. The solvent was then removed by evaporation and the remaining fat weighed. Individual variations of considerable magnitude in the results obtained by the two methods may be found, but in general the correlation was satisfactory for the purpose, particularly when considerable amounts of fat were present.

That variations in the distribution of fat within a given fatty liver exist has been found by Chaikoff and Kaplan [18] (1937) and is also illustrated by data from our own experiments (table 2). In our experience, however, these variations were so slight as to be of no consequence in interpreting the effect of the deprivation of lipocaic on therapy.

## INCIDENCE OF FATTY CHANGES IN THE LIVER IN DEPANCREATIZED DOGS TREATED WITH REGULAR INSULIN AND WITH PROTAMINE ZINC INSULIN

In discussing the papers of Dragstedt, Van Prohaska and Harms, Wilder and Wilbur [19] (1937) made the suggestion:

> That the discontinuous action of insulin, when readily soluble (regular) insulin is given by infrequent injection, may be responsible for the hepatic degeneration of depancreatized animals and that pancreas and derivatives of pancreas given by mouth could owe their curative and preventive properties to some action whereby a more continuous insulin effect is maintained.

TABLE 2.—*Distribution of Fat as Determined by Chemical Analysis in Different Portions of the Liver of Depancreatized Dogs (Specimens Secured at Autopsy)*

| Animal No. | Lobe 1 Fat, % | Lobe 2 Fat, % | Lobe 3 Fat, % | Lobe 4 Fat, % | Lobe 5 Fat, % | Average |
|---|---|---|---|---|---|---|
| 976 | 5.7 | 6.1 | 6.2 | 6.8 | .... | 6.2 |
| 678 | 9.8 | 9.7 | 9.1 | 9.1 | 10.8 | 9.7 |
| 276 | 46.3 | 42.5 | 43.4 | 41.1 | .... | 43.3 |
| 955 | 6.1 | 6.8 | 6.4 | 6.5 | .... | 6.45 |
| 38 | 24.6 | 24.2 | 23.8 | 29.8 | 26.6 | 25.8 |
| 809 | 26.2 | 25.6 | 26.1 | 23.7 | .... | 25.4 |
| 330 | 20.2 | 17.9 | 20.5 | 20.1 | .... | 19.7 |
| 967 | 4.6 | 5.3 | 5.0 | 4.5 | .... | 4.85 |
| 95 | 22.0 | 29.3 | ... | ... | .... | 25.6 |

Such an explanation, if correct, would simplify the situation considerably. The available data from our laboratory, however, indicate that the incidence of fatty infiltration of the liver in depancreatized dogs treated with protamine zinc insulin [20] is just as great as in those treated with regular insulin. From Jan. 1, 1935, to Jan. 1, 1937, the depancreatized animals in our laboratory were treated with regular insulin. From Jan. 1, 1937, to May 1, 1938, protamine zinc insulin was used, and from this time to the present we have used regular insulin. In all, 154 animals have been depancreatized. Of these, fatty changes in the liver which could be attributed to lipocaic deficiency developed in 116. In 13 the liver remained normal, although these were observed long enough for a fatty liver to appear within the usual time. Twenty-five of the animals died

18. Chaikoff, I. L., and Kaplan, A.: J. Biol. Chem. **119**:423, 1937.

19. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **59**:329 (Feb.) 1937.

20. All insulin used in this study was furnished by Eli Lilly & Co.

soon after the operation or were used for other types of experiment, so that data concerning the appearance of the fatty changes in these are not reliable. Thus, in our experience fatty changes in the liver which may be attributed to lipocaic deficiency occur in about 90 per cent of insulin-treated depancreatized dogs. Data with respect to the extent of the fatty infiltration in the liver and the time of onset were obtained by several criteria of lipocaic deficiency, namely: (1) rate of decrease of dextrose excretion, (2) rate of decrease in insulin requirement or tolerance, (3) loss of appetite and decreased activity, (4) hepatic function determined by the bromsulphalein test and (5) results of microscopic and chemical examination of a representative section after laparotomy, inspection of the liver and removal. For 31 animals given regular insulin on which complete data were secured, biopsy specimens of the liver were obtained an average of thirty-six days after pancreatectomy. Nine of these showed an average of 37.3 per cent (4 plus); 12, 22.1 per cent (3 plus); 9, 14.1 per cent (2 plus), and 1, 11 per cent (1 plus) fat in the liver. For 20 animals given protamine zinc insulin on which complete data were obtained, biopsy specimens of the liver were secured an average of thirty-six days after pancreatectomy. Four of these showed an average of 38.3 per cent (4 plus); 10, 24.4 per cent (3 plus); 3, 13.4 per cent (2 plus), and 3, 9.5 per cent (1 plus) fat in the liver. It is thus evident that there is no significant difference between the animals given regular insulin and those given protamine zinc insulin in respect to the time of onset of the fatty changes in the liver or their severity.

The use of protamine zinc insulin provides better control of the diabetes in the sense that a constant absorption of small amounts produces a state more nearly simulating normal than is secured by the use of regular or soluble insulin. The same incidence of fatty liver in the two series is further evidence that the type of fatty infiltration involved here is not due to poor control of the diabetes. It is difficult to avoid hypoglycemic convulsions when protamine zinc insulin is employed in the treatment of experimental diabetes, largely because of variations in the amount of food ingested by the animal from day to day and of a cumulative effect of the slowly absorbed insulin. These convulsions are much more difficult to treat than those occurring with regular insulin therapy and occasion a considerable mortality. For this reason we have returned to the use of regular or soluble insulin.

### EFFECT OF THE ORAL ADMINISTRATION OF INSULIN ON THE DEVELOPMENT OF FATTY LIVER IN THE DEPANCREATIZED DOG

Can the beneficial effect attributed to lipocaic be accounted for on the basis of an unknown action of insulin given by mouth? Will the presence of insulin in the intestine prevent fatty infiltration of the liver in

depancreatized dogs? In our first preparations of lipocaic varying amounts of insulin were undoubtedly present. For these reasons the following experiment was performed: On Feb. 3, 1936, an animal was submitted to total pancreatectomy and placed on a diet of bread, whole milk, meat, cod liver oil and brewers' yeast. Regular insulin was given. On Feb. 29, 1936, a laparotomy was done and the liver seen to be fatty on gross and microscopic inspection; a section contained 32 per cent fat by chemical examination. An adequate dose of lipocaic was then added to the previous diet, and on March 29, 1936, a third laparotomy was done. The liver was found to be normal. Fifty milligrams of dried powdered insulin, containing 1,200 units, was then substituted for the lipocaic and fed with the regular diet for thirty-six days. On May 4, 1936, a fourth laparotomy was done and the liver was found again to be fatty (38.4 per cent). On May 9, 1936, the animal died, and autopsy confirmed the extensive fatty infiltration and degeneration in the liver. The results of this one experiment were so definite and the amount of insulin used so large that it seemed unnecessary to repeat it. It is interesting that the oral administration of this tremendous dose of insulin had no effect whatever on the dextrose excretion, and it is equally apparent that it had no beneficial effect on the fatty infiltration in the liver.

### EFFECT OF CHOLINE AND BETAINE HYDROCHLORIDE ON THE FATTY INFILTRATION OF THE LIVER IN DEPANCREATIZED DOGS

MacLean and Best[21] (1934) reported that the oral administration of choline in doses varying from 1.5 to 2.25 Gm. per day was effective in relieving fatty liver in depancreatized dogs. This observation was confirmed by Van Prohaska, Dragstedt and Harms[18] (1936), who reported a beneficial effect obtained with as little as 1 Gm. of choline daily, but that smaller doses were ineffective. Since this report we have given choline to 6 additional depancreatized dogs, with the following results: Four of the animals were placed on a diet of bread, milk, meat, cod liver oil and brewers' yeast, and the glycosuria was partially controlled with regular insulin. One animal, whose liver on biopsy showed fat, 2 plus (13.4 per cent), was given 200 mg. of choline daily for thirty days, after which a second biopsy disclosed an increase in the amount of fat (3 plus, or 22.2 per cent). This animal was then given 1 Gm. of a fat-free extract of pancreas for twenty-nine days, and at that time the liver was found to be normal. A second animal with a very fatty (4 plus, or 37 per cent) liver was given 500 mg. of choline daily for ten days, after which it died of hypoglycemic convulsions. The fat

21. MacLean, D. L., and Best, C. H.: Brit. J. Exper. Path. **15**:193, 1934.

content of the liver was unchanged. A third animal with a very fatty (4 plus, or 33 per cent) liver was given 700 mg. of choline daily for twenty-eight days, after which a second laparotomy and biopsy disclosed an increase in the fat content to 43 per cent. A fourth animal with a moderately fatty (2 plus, or 14.4 per cent) liver was given 1 Gm. of choline daily for twenty-nine days, after which it died of pneumonia. There was no improvement in the liver. The remaining 2 animals were given a casein diet in addition to the choline and will be considered in the subsequent section.

Most of the observations on the lipotropic action of betaine hydrochloride have been made on dietary fatty liver in rats, and for that reason it seemed advisable to secure additional evidence with respect to its effect on fatty liver in depancreatized dogs. We have given betaine hydrochloride to 4 depancreatized dogs proved to have fatty liver by laparotomy, inspection and biopsy. The results are as follows: All the animals were fed bread, meat, milk, cod liver oil and yeast and given regular insulin. One animal, whose liver at biopsy was fatty (3 plus) was given 2 Gm. of betaine hydrochloride daily for seven days, after which severe convulsions developed and it was electrocuted. The fat content of the liver was unchanged (3 plus). In a second animal, whose liver became fatty (2 plus) in thirty-eight days after pancreatectomy, the condition was controlled for four months by a preparation of lipocaic, and at the end of this time the liver was only slightly fatty (1 plus). The animal was then given 2 Gm. of betaine hydrochloride daily for forty-three days, after which laparotomy and biopsy disclosed an increase in the liver fat (3 plus). The gradual decrease in dextrose excretion and the reduction in insulin requirement also indicated that this amount of betaine hydrochloride was ineffective. A third animal, whose liver was moderately fatty (2 plus, or 12 per cent), was given 3 Gm. of betaine hydrochloride daily for twenty-one days. After this time the various criteria of lipocaic deficiency indicated that the condition of the animal was getting worse, and biopsy of the liver indicated an increased fat content (17 per cent). The fourth animal was found to have a moderately fatty liver (2 plus, or 14 per cent) when examined eighty-nine days after pancreatectomy; 3 Gm. of betaine hydrochloride daily was then given for twenty-four days, with definite clinical improvement and decrease in the liver fat to 1 plus. The same dose was continued then for sixty-five days, after which the liver was found to be entirely normal (fat content, 6.3 per cent). The administration of betaine hydrochloride was then stopped. Within two weeks the sugar excretion decreased markedly, and the dose of insulin had to be reduced. Two months after medication was stopped, the bromsulphalein test revealed moderate impairment of hepatic function, and biopsy after three months revealed

a definite return of fat in the liver, to 3 plus, or 21 per cent. At this time the blood lipids had decreased to 450 mg. per hundred cubic centimeters, or less than half the normal value.

### EFFECT OF CASEIN AND OF VARIATIONS IN DIET ON THE FATTY INFILTRATION OF THE LIVER IN DEPANCREATIZED DOGS

In 1932 Best, Hershey and Huntsman [12d] demonstrated that a diet of mixed grain and 40 per cent beef fat would produce a marked fatty infiltration in the liver of normal rats. This type of dietary fatty liver was found to be prevented by the addition of small amounts of choline to the food (Best and Huntsman; [12e] Best and Ridout; [12f] Best, Channon and Ridout [12a]). Casein was later found to exert a similar lipotropic effect (Best and Huntsman; [22] Channon and Wilkinson; [23] Beeston, Channon and Wilkinson [24]). Best, Grant and Ridout [25] (1936) produced fatty liver in rats by feeding a diet containing 40 per cent fat and 10 per cent casein. When the percentage of casein was raised to 30 or above, no fat accumulated in the liver. The fatty liver produced by the low casein, high fat diet could be prevented by the addition of 10 mg. of choline per rat daily. The authors suggested that 1 Gm. of casein exerts an effect comparable to that of 5 or 6 mg. of choline. In a similar experiment Channon, Loach, Loizides, Manifold and Soliman [26] (1938) estimated that 1 Gm. of caseinogen has an effect equivalent to that of 7 to 8 mg. of choline.

In 1937 MacKay [27] reported that an extract of pancreas prepared as described by Dragstedt, Van Prohaska and Harms was effective in preventing and in curing the type of fatty infiltration of the liver that occurs in rats on a low protein, high fat diet. This finding was confirmed by Aylward and Holt [15] (1937) and by Best and Ridout [28] (1938). Both groups, however, concluded that the effect of the pancreas extract in this connection could be accounted for on the basis of its choline and protein content. MacKay and Barnes [29] (1938) came to a similar conclusion. On the other hand, Channon, Loach and Tristram [30]

22. Best, C. H., and Huntsman, M. E.: J. Physiol. **83**:255, 1935.
23. Channon, H. J., and Wilkinson, H.: Biochem. J. **29**:350, 1935.
24. Beeston, A. W.; Channon, H. J., and Wilkinson, H.: Biochem. J. **29**:2659, 1935.
25. Best, C. H.; Grant, R., and Ridout, J. H.: J. Physiol. **86**:337, 1936.
26. Channon, H. J.; Loach, J. V.; Loizides, P. A.; Manifold, M. C., and Soliman, G.: Biochem. J. **32**:976, 1938.
27. MacKay, E. M.: Am. J. Physiol. **119**:783, 1937.
28. Best, C. H., and Ridout, J. H.: Am. J. Physiol. **122**:67, 1938.
29. MacKay, E. M., and Barnes, R. H.: Proc. Soc. Exper. Biol. & Med. **38**: 410, 1938.
30. Channon, H. J.; Loach, J. V., and Tristram, G. R.: Biochem. J. **32**:1332, 1938.

(1938), using similar methods, came to exactly the opposite conclusion. They stated:

> Eight assays of the activity of the five pancreatic extracts used were made; all of them showed the extracts to possess an ability to prevent fat deposition in the liver greater than could be attributed to their content of choline. The average value for this non-choline activity was equivalent to that of 426 mg. of choline per 100 Gm. pancreas while the choline present in the extracts accounted for only one-third of their activity. The non-choline activity is not accounted for by the protein content of the extracts and it is concluded that there exists in pancreas a substance other than choline which is involved in fat deposition in the liver.

We have made no observations on the effect of lipocaic on dietary fatty liver in rats. It should perhaps be pointed out, however, that fatty infiltration of the liver in animals may be produced in a great variety of ways and the significance of each state not be the same. A failure to demonstrate a lipotropic effect of lipocaic on dietary fatty liver in otherwise normal rats when the pancreas is intact can hardly be advanced as evidence against its effect on a specific defect in the depancreatized dog until it is clearly demonstrated that the disturbance in each case is the same. The positive findings of Professor Channon are therefore of special interest and significance.

In view, however, of the clearcut demonstration of the marked effect which choline and certain proteins, notably casein, have on dietary fatty liver in rats, it seemed important to us to secure some evidence with respect to the effect of these substances both singly and in combination on the depancreatized dog.

The stock diet most commonly used in this laboratory has been made up of white bread, whole milk, beef muscle and bone meal, plus small amounts of cod liver oil and brewers' yeast. The fat content of this diet is approximately 25 per cent. In our experience dogs take this diet more readily than others and may be maintained in excellent nutrition in laboratory cages for four or five years. In our first experiments [3] yeast and cod liver oil were not added to the diet. Chaikoff and Kaplan [14] (1937) have suggested that the early appearance of fatty liver and the relatively short survival period of depancreatized dogs fed this diet may be due to vitamin deficiency. The prompt recovery of these animals when given a fat-free alcoholic extract of pancreas, however, speaks against this view. It has seemed wise to add the vitamin supplements, nevertheless, although to date such addition has not altered the picture appreciably. The suggestion of Himwich [31] (1938) that failure to secure long survival of depancreatized dogs fed this diet is due to inadequate absorption does not seem valid in view of the fact pointed out in our previous report [13] that the addition of large amounts of fresh active

31. Himwich, H. E., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1938, vol. 7, p. 143.

pancreatic juice, which improves digestion and absorption, nevertheless does not delay the appearance of fatty liver or prolong life. Indeed, in view of the results to be reported later, it seems more likely that the better absorption of fat secured by the feeding of pancreatic juice has led to a more rapid accumulation of fat in the liver and to a decrease in the period of survival.

In the following experiments three diet mixtures have been employed, the compositions of which are indicated in table 3. Cowgill's [32] casein III diet was selected because in the experience of that investigator the formula has been found to be balanced and adequate for dogs. It was

TABLE 3.—*Composition of Special Diets Fed to Depancreatized Dogs*

| | Percentage |
|---|---|
| **(1) Cowgill's (1936) Casein III Diet (Modified)** | |
| Casein, commercial (12.7% N) | 38.45 |
| Sucrose | 27.45 |
| Bone ash | 2.45 |
| Salt mixture* | 1.22 |
| Lard | 22.03 |
| Cod liver oil | 1.87 |
| Brewers' yeast | 6.53 |
| **(2) High Casein, Low Fat Diet** | |
| Casein | 45 |
| Sucrose | 45 |
| Bone ash | 3 |
| Salt mixture* | 1 |
| Cod liver oil | 2 |
| Brewers' yeast | 4 |
| **(3) Low Casein, High Fat Diet** | |
| Casein | 26.6 |
| Sucrose | 19.0 |
| Salt mixture* | 1.3 |
| Bone ash | 2.6 |
| Lard | 44.1 |
| Cod liver oil | 2.0 |
| Brewers' yeast | 4.4 |

* Formula for the salt mixture: sodium chloride, 25%; potassium chloride, 25 %; calcium lactate, 22.5%; magnesium citrate, 22%; ferric citrate (finely ground), 5%; potassium iodide, 0.5%.

fed to 7 depancreatized dogs, usually with the addition of 400 cc. of milk to make the mixture more palatable, and from 100 to 300 cc. of pancreatic juice daily. One dog failed to show a fatty liver and remained in good condition. The other 6, however, were no different from the animals on the bread, meat and milk diet. The fatty infiltration in the liver appeared just as rapidly and was equally severe. In 1 additional animal the effect of choline was investigated. This animal was depancreatized and placed on a diet of bread, meat, milk, bone meal, brewers' yeast, cod liver oil and 200 cc. of pancreatic juice daily. Laparotomy and biopsy at the end of thirty days revealed a fatty liver graded 2 plus. Cowgill's casein III diet was then given and a potent preparation of

32. Cowgill, G. R.: Personal communication to the authors.

lipocaic added. Biopsy in twenty-eight days revealed a normal liver. One gram of choline daily was then substituted for the lipocaic and the casein III diet continued as before. Laparotomy and biopsy in sixteen days revealed a reaccumulation of fat in the liver, graded 4 plus.

The low casein, high fat diet was fed to 4 depancreatized dogs. These animals were also given supplementary feedings of fresh pancreatic juice daily in amounts of from 100 to 300 cc. Marked fatty liver developed in 3, in each somewhat sooner than in animals fed the stock diet. An abbreviated protocol for the fourth animal is supplied, because it illustrates a beneficial result obtained with choline.

*Dog 663.*—On July 27, 1936, pancreatectomy was done and a diet of bread, milk, meat, bone meal, yeast and cod liver oil given, with regular insulin and 100 cc. of pancreatic juice daily. On September 8 biopsy showed 3 plus fat in the liver. From Sept. 8 to Jan. 4, 1937, the aforementioned diet was continued, with addition of a potent preparation of lipocaic. On January 4 laparotomy and biopsy showed the liver normal. From January 5 to 19 Cowgill's casein III diet, 160 Gm., plus 400 cc. of milk and 200 cc. of pancreatic juice was given daily. From January 19 to February 8 a low casein, high fat diet plus 400 cc. of milk and 200 cc. of pancreatic juice was given daily. On February 8 biopsy showed 4 plus fat in the liver. From February 10 to March 9 a low casein, high fat diet plus milk and pancreatic juice and 2 Gm. of choline was given daily. On March 9 biopsy showed the liver normal.

The high casein, low fat diet was fed to 3 depancreatized dogs. The effects are indicated in the following abbreviated protocols:

*Dog 269.*—On March 22, 1937, pancreatectomy was done, and a diet of bread, meat, milk and vitamin supplements with pancreatic juice, 100 cc., and protamine zinc insulin was given. On April 23 biopsy showed 3 plus fat in the liver. From that date to May 2 the high casein, low fat diet with pancreatic juice but no milk was given. On May 2 the dog died in convulsions (presumably hypoglycemic). Autopsy showed the liver normal.

*Dog 104.*—On Jan. 25, 1937, pancreatectomy was done, and a diet of bread, milk, meat and vitamin supplements was given, with 70 cc. of pancreatic juice daily and protamine zinc insulin. On March 2 biopsy showed 1 plus fat in the liver. From March 2 to April 9 the high casein, low fat diet plus 400 cc. of milk and 50 cc. of pancreatic juice was given. On April 9 biopsy showed 1 plus fat in the liver. From April 9 to 19 a diet of bread, meat, milk and vitamin supplements was used. On April 19 the animal died of hypoglycemic convulsions. Autopsy showed 3 plus fat in the liver.

(A beneficial effect of the high casein, low fat diet on this animal was indicated by the increased dextrose excretion and increased insulin tolerance during this period, with no increase in liver fat. A blood lipid content of 420 mg. per hundred cubic centimeters on February 4, of 520 mg. on February 17 and of 880 mg. on March 17 confirmed this view.)

*Dog. 47.*—On Jan. 22, 1937, pancreatectomy was done and a diet of bread, meat, milk and vitamin supplements given, with 80 cc. of pancreatic juice daily and protamine zinc insulin. On March 2 biopsy showed 2 plus fat in the liver. From March 2 to April 9 the high casein, low fat diet plus 400 cc. of milk and 100 cc.

of pancreatic juice was given. On April 9 biopsy showed the liver normal. Dextrose excretion and insulin tolerance were increased. From that date to August 12 the high casein, low fat diet plus 100 cc. of pancreatic juice but no milk was given. On August 12 biopsy showed 2 plus fat in the liver.

The additional evidence secured in these experiments indicates that approximately 2 Gm. of choline per day over and above that contained in the diet is required to prevent or relieve the fatty infiltration of the liver that occurs in depancreatized dogs. This agrees with the findings of Ralli, Rubin and Present [33] (1938), who reported that even this amount may not be uniformly effective in preventing some degree of fatty infiltration. It seems equally clear that a high fat, low protein diet facilitates, and a low fat, high protein diet delays, the appearance of fat in the liver in these animals when pancreatic juice is also provided to improve the digestion and absorption of the food. It is probable that the proportion of fat in the diet is of greater significance in this connection than the amount or quality of protein and its possible lipotropic action. Thus Cowgill's casein III diet, which contained 38 per cent casein and 24 per cent fat, did not delay the appearance of fat in the liver more than the bread, meat and milk diet, which contained 25 per cent fat. One gram of choline daily in addition to the diet containing 38 per cent casein did not prevent the development of fatty liver in an animal proved to be susceptible and in which on a previous trial 2 Gm. of a fat-free alcoholic extract of pancreas was effective. When the casein level was reduced to 27 per cent and the fat raised to 46 per cent, fat deposition in the liver was definitely accelerated. Although more data are obviously required, the diet high in casein and low in fat did definitely retard the appearance of fat in the liver and improve the clinical condition of the animals. It seems likely that such a diet may lessen the need for lipocaic, and this, if true, would be of great significance with respect to the function of this substance. In this connection it is of interest that the diet used by Chaikoff and Kaplan [14] (1937), on which an unusually long survival was secured, contained relatively little fat, only that present in raw lean beef apparently being ingested.

### SOME PREPARATIONS OF LIPOCAIC AND THEIR CHOLINE CONTENT

In the initial experiments reported by Dragstedt, Van Prohaska and Harms [8] (1936) the activity of pancreas was found to be retained in alcoholic extracts freed from fat by extraction with ether. In view of the fact that insulin is obtained by a somewhat similar procedure, whereas the beneficial action of pancreas in this particular is not exerted by insulin, it seemed desirable to determine, if possible, where lipocaic

33. Ralli, E. P.; Rubin, S. H., and Present, C. H.: Am. J. Physiol. **122**:43, 1938.

was lost in the extraction of pancreas for the preparation of insulin. In this attempt we secured the help of Drs. G. H. A. Clowes and George B. Walden, of Eli Lilly & Co., who prepared numerous pancreatic fractions. In the preparation of insulin, fresh pancreas may be extracted with alcohol acidified with sulfuric acid. As near as we can estimate by our methods, approximately three fourths of the lipocaic in the pancreas appeared in the acid alcohol and one fourth remained in the residue. The dried residue was administered to 8 depancreatized dogs and in 3 of these was found to be effective in a dose of 10 to 20 Gm. per day. Hot water extracts of this pancreatic residue were given to 5 depancreatized dogs and were found to be effective in a dose of 3 to 4 Gm. of dried material. These extracts were examined by Dr. Edward Eagle and found to contain between 3 and 4 mg. of free choline per gram of dried substance. The estimations of choline were made by the method of Ambo and Aoki,[34] as modified by Eagle. Dr. Eagle also made the subsequent determinations of choline in the pancreatic extracts described in this paper. The acid-alcohol extract of the whole pancreas may be partially evaporated to drive off the alcohol and the remaining acid-water solution concentrated by evaporation and chilled and the fat skimmed off. The addition of a mixture of strong alcohol and ether to the preparation in the acid-water phase results in the formation of a precipitate. This, when dried, has been found to be effective in a dose of 0.75 to 1.5 Gm. per day. This extract was found to contain 0.131 mg. of choline per gram of dried substance. In the acid-water phase of the insulin-forming procedure the substance may be concentrated by evaporation and raised to 80 per cent alcohol concentration by the addition of strong alcohol. A precipitate relatively free from insulin forms and has been found to contain an effective dose of lipocaic in from 2 to 3 Gm. of dried substance. Examination of three different preparations revealed less than 1 mg. (0.604, 0.209 and 0.314 mg.) of choline per gram of extract. These three preparations were dialyzed against distilled water through a celloidin membrane for from two to six weeks. The non-dialyzable fraction revealed the characteristic activity of lipocaic, whereas the dialyzate was found to be inert. If in the acid-water phase of the insulin extraction the substance is saturated with ammonium sulfate or with sodium chloride, both insulin and lipocaic may be thrown out as a precipitate. In the further steps in the preparation of insulin it seems probable that lipocaic is lost, owing to the fact that insulin is soluble in the higher concentrations of alcohol whereas lipocaic seems to be insoluble in alcohol of over 70 per cent concentration under the conditions of our experiments.

As noted in the previous section, the conclusion that the lipotropic effect of pancreas can be accounted for on the basis of its choline or

34. Ambo and Aoki: Tr. Jap. Path. Soc. **21**:171, 1931.

choline plus protein content has been based almost entirely on experiments on the type of fatty infiltration of the liver that occurs in normal rats fed a diet low in protein and rich in fat. The pancreas in these animals is intact, and it would seem reasonable to expect that the "factors of safety" involved in its function should be adequate to meet rather wide variations in dietary composition without a defect similar to that which obtains when the pancreas is removed resulting. While it may be true that the fatty liver produced by diet in the rat is the same as that produced by depancreatizing the dog, it would seem unwise, in the present state of knowledge, to apply conclusions derived in the former case to the specific defect present in the latter.

The evidence that choline is not the substance in pancreas which accounts for its beneficial action in preventing and relieving fatty infiltration of the liver in the depancreatized dog and in permitting the animal to survive for a long period when treated with adequate insulin also may be summarized as follows:

1. It requires approximately 2 Gm. of choline per day over and above that present in the diet to exert this beneficial effect, whereas 100 Gm. of pancreas, which is an effective dose, contains only about 250 mg. of choline.

2. Liver and brain, which contain as much or more choline, exert no beneficial effect.

3. When extracts of pancreas are made, the active substance appears in the fat-free alcoholic extracts, whereas the ether-soluble fractions, which contain practically all the lecithin of the pancreas and accordingly almost all the choline, are inert.

4. It has been possible to secure fat-free extracts of pancreas effective in a dose of 1 to 2 Gm. of dried substance per day and containing not more than a few milligrams of choline per gram of dried substance.

## SUMMARY AND CONCLUSIONS

The demonstration that lipocaic is an internal secretion of the pancreas depends on the recognition that the depancreatized dog fed on a mixed diet of protein, carbohydrate and fat is not restored to a normal state by the adequate administration of insulin and pancreatic juice, and that the remaining deficiency is corrected by the oral administration of pancreas or of certain extracts of pancreas but not of other organs.

Two types of fatty infiltration of the liver occur both in diabetes mellitus and in pancreatic diabetes. One type is due to poor control of the diabetes by inadequate administration of insulin and is characterized by a normal or high concentration of the blood lipids and acidosis and is relieved by better insulin therapy. The second type is due to

lipocaic deficiency and is characterized by a low concentration of the blood lipids, impaired hepatic function and decreased dextrose excretion and insulin sensitivity and is relieved by lipocaic therapy but not by insulin.

In 92 per cent of 154 depancreatized dogs in our laboratory fatty infiltration of the liver developed; in the remaining 8 per cent the liver remained normal.

All of a series of 12 depancreatized dogs that were fed a mixed diet of protein, carbohydrate and fat and treated with insulin but given no supplement other than pancreatic juice died with fatty liver within three months.

For the assay of a pancreas fraction for lipocaic, it is suggested that a minimum of 3 depancreatized dogs be placed on a mixed diet of carbohydrate, protein and rather liberal amounts of fat and given sufficient insulin to permit a urinary excretion of dextrose of not more than 5 Gm. per day. Lipocaic deficiency may be concluded to be present at the end of four to six weeks in the presence of the following symptoms and findings: decrease in appetite and activity, decrease in dextrose excretion, decrease in insulin requirement to 5 units or less per day with occasional hypoglycemic convulsions on this dose, 10 to 20 per cent retention of bromsulphalein twenty minutes after the intravenous injection of the dye and decrease in the concentration of the blood lipids to levels of 500 to 300 mg. per hundred cubic centimeters—all to be confirmed by laparotomy, inspection of the liver and removal of a representative section for microscopic and chemical examination. That the dose of lipocaic is adequate may be concluded after administration of the test fraction for four to six weeks by disappearance of these abnormalities, checked again by laparotomy, inspection and biopsy of the liver.

The distribution of fat in the liver in depancreatized dogs is found to be sufficiently uniform to justify attaching definite significance to the detection of fat in a single biopsy specimen.

A comparison of the estimation of fat in the liver by histologic and by chemical methods is given.

Better control of the diabetes by the use of protamine zinc insulin does not delay or decrease the incidence or severity of fatty infiltration of the liver in depancreatized dogs.

The oral administration of 1,200 units of insulin daily for thirty-six days did not affect the onset or extent of fatty changes in the liver of a depancreatized dog.

The oral administration of 3 Gm. of betaine hydrochloride daily was found to be effective in relieving fatty liver in depancreatized dogs, but smaller doses, such as 2 Gm., were ineffective.

At least 2 Gm. of choline daily over and above the amount present in the diet is required to relieve fatty liver in depancreatized dogs. One gram of choline daily in addition to a diet containing 38 per cent casein did not prevent the development of typical fatty liver.

The substitution of casein as the source of protein in the diet of the depancreatized dog does not prevent or delay the appearance of fatty liver.

High fat, low protein diets accelerate, and low fat, high protein diets delay, the appearance of fatty liver in depancreatized dogs.

It has been possible to secure fat-free alcoholic extracts of pancreas containing an adequate dose of lipocaic in 1 Gm. of the dried substance and containing not more than a few milligrams of choline per gram.

It seems probable that lipocaic is removed from the usual preparation of insulin, since insulin is soluble and lipocaic is insoluble in alcohol when the concentration reaches 90 per cent.

# STRUCTURAL CHANGES IN THE LUNGS OF DRUG ADDICTS

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In reviewing thoracic roentgenograms taken routinely of several thousand drug addicts admitted to the Riker's Island Hospital in the past few years, a number of varied and interesting findings were noticed. These, as will be shown later, appeared to be entirely at variance with the patients' complaints and their clinical course. They also varied in intensity almost directly with the period during which the drugs had been used.

The addicts were subjected to a six day reduction regimen immediately on their admission to the hospital. Roentgen examination of almost all of them was done on the fourth or fifth day after the commencement of the period of withdrawal of the drug. This usually corresponds to the time in which symptoms due to withdrawal begin to wane and the patient feels comparatively comfortable. Roentgen examination of a few was done during the height of these symptoms, which occurs usually on the second day after the beginning of the reduction period. In the latter group the pulmonary changes were most pronounced.

Before any conclusions were drawn from observations as to the relation between the use of drugs such as cocaine and opium and its alkaloids and their possible effects on parenchymal pulmonary changes, a search of the literature was made for the purposes of studying the pharmacology and the physiology of the drugs in question and of establishing, if possible, physiologic principles on which the clinical observations might be based. Although this search did not disclose similar observations, it provided me with important clinical experimental data which substantiate my own findings and the conclusions I intend to set forth.

## ANALYSIS OF CLINICAL DATA

During the past fifteen months roentgen examination of the chests of 674 male addicts was done, in most instances after and in a few during the height of the symptoms caused by withdrawal of the drug. One hundred ambulatory drug addicts were studied for the purpose

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of determining the status of the upper respiratory tract. The investigation consisted of routine examinations of the sinuses by means of transillumination; roentgen examination of the sinuses was done in 50 cases. The teeth, tonsils, pharynges and nasal septums were inspected. In 80 other cases the changes were observed accidentally in the hospital after the development of acute illness.

The addicts may be divided into two classes: (1) those who entered the hospital voluntarily and (2) those who were imprisoned after conviction for crimes not necessarily connected with the use of drugs.

TABLE 1.—*Summary of Clinical Data*

| | |
|---|---|
| Number of patients | 674 |
| Age, years | |
| Youngest | 17 |
| Oldest | 62 |
| Average | 39 |
| Period of addiction | |
| Shortest period | Three months |
| Longest period | Thirty-nine years |
| Average | Eighteen years |
| Kind of Drugs Employed | |
| Heroin, opium, morphine, cocaine, laudanum, hashish, cannabis, sodium amytal and pentobarbital sodium | |
| Methods of introduction | |
| Subcutaneous, intravenous, inhalation and oral | |
| Period of Observation | |
| From the third to the sixth day of the withdrawal period | |
| A few during the height of the withdrawal symptoms | |
| Method of treatment | |
| All patients were treated by progressive withdrawal over a six day period | |

Most of them had apparently acquired the habit during adolescence and had continued it consistently except for brief intermissions which usually occurred because of imprisonment or lack of funds. After each of these intervals the habit would be resumed more relentlessly. The youngest addict was 17 years old, the oldest was 62 and the average age was 39. At the time of observation the duration of addiction ranged, according to the addicts, from three months to thirty-nine years. The average was eighteen years. Almost all of the patients had taken more than one drug at some time. Heroin (diacetylmorphine) was the drug most commonly employed. This was partly due to the fact that it is more accessible and, according to the addicts, less expensive. Opium and its derivative morphine were next in order among the drugs

used. Cocaine, contrary to popular conception, was used comparatively less than the others. A few employed so-called "bombshells" or "speed balls," which usually contained a mixture of morphine and cocaine and were taken subcutaneously. In addition, some admitted having used hashish, cannabis, laudanum and marijuana (cannabis). A few supplemented the drugs mentioned with sedatives, such as sodium amytal and pentobarbital sodium. One prisoner, a Chinese, acquired, while in prison, the probably unique habit of smoking powered aspirin (acetylsalicylic acid). This he readily secured from the attendants by complaining of constant headaches. When given phenyl salicylate instead, he showed an uncanny instinct in recognizing that it was not aspirin.

Most of the drugs were taken subcutaneously. Other routes, in the order of frequency: (1) intravenous injection (addicts using this method are the so-called "main line shooters"), (2) smoking of opium and (3) inhalation, usually of cocaine. The majority of the patients had employed combinations of drugs as well as more than one avenue of introduction.

The addicts represented every stratum in the social scale. However, the majority belonged to the lower classes. It must be remembered that most drug addicts display psychopathic trends and are particularly giving to lying. Information elicited from them, therefore, is not necessarily accurate.

A definite routine was followed in all cases. Immediately on the patient's admission to the hospital a brief but pertinent history was elicited with reference to age, past illnesses, duration of the habit, periods of interruption and kind or kinds of drugs used. The withdrawal treatment to which the addicts were subjected consisted of subcutaneous injections of progressively diminished quantities of morphine sulfate. The entire withdrawal treatment lasted only six days. The usual symptoms were observed and were regarded with equanimity. However, when other signs and symptoms occurred, as they frequently did, they were treated accordingly. At the end of the six day period each patient was automatically transferred to another part of the hospital to receive custodial care and to serve the usual sentence of one hundred days.

## ROENTGEN FINDINGS

Of the 674 patients the thoracic roentgenograms of only 92 (13.5 per cent) were entirely normal. The remainder (86.5 per cent) showed various abnormalities. The commonest abnormality consisted of pulmonary changes characteristic of hypertrophic emphysema,[1] i. e.,

1. Assmann, H.: Die klinische Roentgendiagnostik der inneren Erkrankungen, ed. 5, Leipzig, F. C. W. Vogel, 1932. Sante, L. R.: The Chest Roentgenologically Considered, New York, Paul B. Hoeber, Inc., 1930.

voluminous lung fields, prominent hilar shadows, diffuse, increased vascular markings (due to peribronchial and perivascular thickening as well as to fine interstitial fibrosis); an outline, usually of the right interlobar fissure, between the upper and middle lobes; obliteration of one or both costophrenic sinuses, and tenting and occasionally distortion of one or both diaphragmatic domes (fig. 1). The group in which these changes were present numbered 207 patients (30.7 per cent), most of whom had used drugs from fifteen to twenty years. Another group, of 94 patients (13.94 per cent), merely showed signs of emphysema (fig. 2) without generalized increase in pulmonary markings.[2]

Fig. 1.—Roentgenogram of the chest of a drug addict.

In a small group there were increased markings with slight signs or no signs of emphysema. These patients numbered 32 (4.74 per cent). The addicts in this group had, according to their history, a short period of addiction, from three months to five years (fig. 3).

The remainder of the addicts (149, or 39.12 per cent) displayed, in addition, the following changes (table 2): fibroindurative tuberculosis of one or both apexes and occasionally of the subapical regions, minimal apical scarring, fibrocaseous pneumonic tuberculosis, calcified

2. Rabin, C. B.: Diagnostic Roentgenology, in Nelson Loose Leaf Living Medicine, New York, Thomas Nelson & Sons, 1936, vol. 1, pp. 91-93.

Fig. 2.—Roentgenogram of the chest of a man aged 43 who had been addicted to the use of heroin (diacetylmorphine) for twenty years.

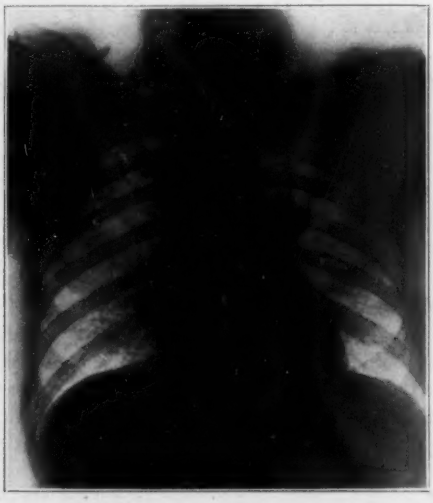

Fig. 3.—Roentgenogram of the chest of a man aged 30 who had been addicted to the use of heroin (diacetylmorphine) for three years.

tuberculosis of one or both upper lobes, bronchiectasis, calcareous pleuritis, interlobar effusion (1 case) and emphysema bullosum (1 case).

In a few cases roentgen examination was done during the height of symptoms caused by withdrawal of the drug. It is interesting to note that in these there was marked accentuation of the thoracic findings and that the serial roentgenograms invariably showed some regression after the symptoms subsided (fig. 4).

The cardiac shadow was invariably small and the cardiothoracic ratio [3] altered except in cases in which hypertensive or other heart dis-

TABLE 2.—*Summary of Roentgen Findings*

| Condition | Number of Cases | Percentage |
|---|---|---|
| Normal | 92 | 13.50 |
| Changes due to hypertrophic emphysema | 207 | 30.70 |
| Emphysema without increased markings | 94 | 13.94 |
| Increased markings without emphysema | 32 | 4.74 |
| Emphysema with obliteration of the right costophrenic sinus | 42 | 6.23 |
| Emphysema with obliteration of the left costophrenic sinus | 19 | 2.81 |
| Emphysema with obliteration of both costophrenic sinuses | 36 | 5.34 |
| Emphysema and thickening of the right interlobar fissure | 66 | 9.75 |
| Emphysema, increased markings and scarring of the apexes | 20 | 2.96 |
| Emphysema, increased markings and bronchiectasis | 6 | 0.89 |
| Fibroindurative tuberculosis without other abnormal features | 5 | 0.74 |
| Fibroindurative tuberculosis with increased markings | 39 | 5.78 |
| Caseous pneumonic tuberculosis bilateral | 3 | 0.44 |
| Calcified tuberculosis of both upper lobes | 7 | 0.04 |
| Calcareous pleuritis, emphysema and increased marking | 3 | 0.44 |
| Calcareous pleuritis without other changes | 1 | 0.14 |
| Emphysema bullosum with increased markings | 1 | 0.14 |
| Right interlobar effusion | 1 | 0.14 |
| Total | 674 | 100 |

ease was present as a complication. Occasionally the pulmonic conus appeared accentuated.

As these structural changes are commonly encountered among nonaddicts and as the coexistence of more than one pathologic process may produce similar changes in the lungs, the following questions naturally arose: First, it is likely that the abnormal pulmonary changes had existed prior to addiction, or that they proved to be merely natural sequelae such as are commonly observed in long-standing infections of the upper respiratory tract? Secondly, is it likely that the pathologic

3. Danzer, S.: Cardiothoracic Ratio, Am. J. M. Sc. **157**:513-521 (April) 1919.

changes were present because of the coexistence of other diseases, namely, allergic diatheses, heart disease, asthma, tuberculosis or bronchiectasis? Thirdly, why were the changes more pronounced in cases in which roentgen examination was done during the period of withdrawal? Was this the result of somatic changes [4] due to deprivation of the drug? Finally, did opium and its derivatives, as well as the other drugs employed, actually produce or enhance the condition? If so, what is the mechanism underlying such an action?

In order to answer these questions it was necessary to examine patients clinically for the purpose of ruling out infectious foci, such as diseased tonsils, carious teeth, infected sinuses and other possible

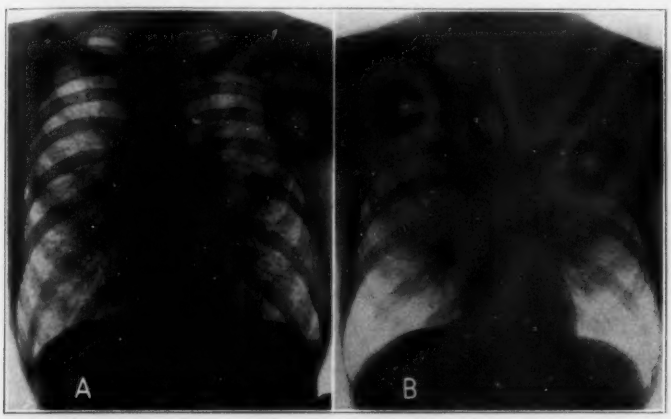


Fig. 4.—Roentgenograms of the chest of a man aged 41 who had been addicted to the use of heroin (diacetylmorphine) for twenty-two years. *A*, film taken at the height of the symptoms which followed withdrawal of the drug; *B*, film taken after these symptoms had subsided.

coexistent conditions, since, according to Mullin [5] and others, these processes may produce identical changes in one of two ways: by lymphatic extension through the right side of the heart into the lungs, or by direct extension from the pharynx to the larynx, trachea and bronchi, thus producing emphysema and bronchiectasis. Again, Light

4. Wuth, O.: Zur pathologischen Physiologie der Morphium-Entziehung, Klin. Wchnschr. **10**:1723 (Sept. 12) 1931.

5. Mullin, W. V.: Relation of Paranasal Sinus Infection to Disease of the Lower Respiratory Tract, J. A. M. A. **87**:739 (Sept. 4) 1926.

and Torrance [6] have shown in their classic work among addicts the following facts: 1. The addicts were all excessive smokers. 2. Their hygiene was poor. 3. They possessed slovenly habits. 4. A good many of them had chronic focal infections.

Two distinct groups, therefore, were investigated: one of patients without any complaints and apparently in good health; the other of patients with complaints and clinical signs sufficient to warrant hospitalization.

### ANALYSIS OF ONE HUNDRED CASES

One hundred cases were analyzed in this group. Routine physical examinations were performed. The average addict was pathetic and somewhat emaciated, without marked external manifestations of specific illness. The frontal sinuses and antrums were examined by means of transillumination. In 50 cases roentgen examination of all the sinuses was done. The remainder of the features of the upper

TABLE 3.—*Summary of Findings in One Hundred Cases*

| Groups | Number of Cases |
|---|---|
| Deviated septums | 37 |
| Dental caries | 29 |
| Diseased sinuses | 23 |
| Enlarged and diseased tonsils | 16 |
| Chronic pharyngitis | 9 |
| Gingivitis | 7 |
| More than one focus of infection | 30 |
| More than two foci of infection | 21 |
| More than three foci of infection | 16 |

respiratory tract were elicited by inspection and auscultation. The following observationns were made: The outstanding abnormality was deviation of the septums (37 cases). Dental caries was next in order (29 cases). This was followed by abnormal sinuses (23 cases), enlarged and diseased tonsils (16 cases), chronic pharyngitis (9 cases) and gingivitis (7 cases). In 63 cases there were no obvious foci. In 16, in addition to deviated septums, involvement of the teeth, tonsils, sinuses and bronchi was present.

Examinationn of the chest invariably disclosed signs of emphysema, namely, enlargement of both diameters, hyperresonance, occasionally

6. Light, A. B., and Torrance, E. G.: Opium Addiction: III. Circulation and Respiration of Human Addicts During Administration of Morphine, Arch. Int. Med. **43**:556 (April) 1929. Karr, W. G.; Light, A. B., and Torrance, E. G.: IV. Blood of Human Addict During Administration of Morphine, ibid. **43**:684 (May) 1929.

limitation of motion of one or both diaphragms, some diminution of breath sounds and heart sounds, rhonchi, sibilant and sonorous rales and in some cases diffuse wheezing throughout both lung fields. In a few instances there were moist rales at the bases of the lungs.

From table 3 it is obvious that the number of cases in which there were possible foci of infection was not more than 37 per cent. It was probably much smaller, for one is not inclined to regard deviation of the septums without other evidence of infectious foci as a competent cause of structural changes in the lungs. One must therefore consider those patients with more than one focus of infection. This group, according to table 3, constituted 30 per cent. When one compares this number with the total number of patients with abnormal thoracic findings, which was 86.5 per cent, one readily sees that the existent foci of infection could not possibly have produced the changes described in so large a number of persons.

The second group consisted of 80 patients who were confined to the hospital for treatment of acute illnesses. This number was treated at various intervals for forty different diseases. Outstanding among these were acute bronchitis, malaria, syphilis, tuberculosis, malnutrition, bronchial asthma, arteriosclerotic heart disease, duodenal ulcer, psychoses and psychopathic personality. The remaining conditions for which the patients in this group were hospitalized are listed in table 4.

A number of patients had more than one disease during their hospitalization; also, some of the same group were readmitted either because of their original complaints or for some other illness which developed during the period of incarceration.

It is interesting to study the more prevalent diseases for which the addicts were treated. For example, table 4 shows a rather small number of diseases referable to the lungs and upper respiratory tract. Syphilitic patients were few. This may be due to the fact that a good many addicts are homosexual. The incidence of malaria is high. This is a well recognized complication, as has been shown by Biggam and by Boyd and Schlachman [7] and others. Only 10 patients with pulmonary tuberculosis were admitted to the hospital. The process was active and the sputum yielded tubercle bacilli in less than half of this number. This is certainly a small percentage and not in harmony with the general conception of the prevalence of tuberculosis among drug addicts who are prison inmates. The incidence of duodenal ulcer was also high and warrants further investigation.

7. Boyd, L. J., and Schlachman, M.: Malaria in Drug Addicts, New York State J. Med. **38**:974 (July 1) 1938.

It has been mentioned that the pulmonary changes were more pronounced in addicts examined by means of the roentgen rays during the height of the withdrawal symptoms. This may be due to a decidedly lowered bodily resistance and possibly to an exacerbation of a chronic infection of the upper respiratory tract, or it may be explained on the basis of somatic changes due to deprivation of the drug. It must be remembered that other unexplained features commonly make their appearance at this stage of the withdrawal period, namely, leukocytosis, glycosuria and albuminuria.

TABLE 4.—*Summary of Acute Diseases in Drug Addicts*

| Disease | Number of Cases |
|---|---|
| Acute bronchitis | 15 |
| Syphilis | 15 |
| Malaria | 15 |
| Pulmonary tuberculosis | 10 |
| Duodenal ulcer | 8 |
| Malnutrition | 7 |
| Arteriosclerotic heart disease | 4 |
| Bronchial asthma | 4 |
| Psychosis and psychopathic personality | 4 |
| Pulmonary emphysema with right heart failure | 2 |
| Bronchopneumonia | 2 |
| Inguinal hernia | 2 |

In addition, 1 case each of the following diseases was observed: Varicosities with ulcers of the lower extremities, acute tonsillitis, cellulitis of the left arm, chronic interstitial nephritis, gastric neurosis, hyperthyroidism, syphilitic heart disease, cerebral edema, acute encephalitis, acute laryngitis, chronic osteomyelitis of the foot, acute catarrhal jaundice, manic-depressive psychosis, acute appendicitis, cerebral arteriosclerosis, acute gastritis, intercostal neuralgia, acute cholecystitis, atrophic cirrhosis of liver, mucous colitis, epigastric hernia, foreign body (needle), hepatosplenomegaly, alcoholism, phimosis, pyorrhea alveolaris, hemorrhoids and regional ileitis.

## ACTION OF MORPHINE

The question whether opium and its derivatives play an important part in the production of structural pulmonary changes in drug addicts will be answered after a review of some of the literature on the action of morphine and experimental work with this drug on lower animals. Morphine was chosen because it is the most representative drug of the opiate series and also because it was commonly used by the addicts.

According to the literature,[8] the action of morphine on respiration is selective. In the nonaddict an increased dose of the drug retards

8. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, ed. 8, Philadelphia, Lea & Febiger, 1924, pp. 245-258.

respiration and increases its amplitude. The latter action is due to the accumulation of carbon dioxide, which stimulates the respiratory center. In drug addicts, unless very large doses of morphine are taken, there is no appreciable variation in the respiratory rate.[6] Minor variations in the respiratory rate, therefore, could not have produced the abnormal pulmonary changes.

A more consequential action of morphine is its effect on smooth bronchial musculature. By direct action, it causes first dilatation and later constriction of the smaller bronchi.[9] The latter is due to an increase in tone of the muscle. (Some pharmacologists believe this to be a peripheral nerve action.) Although this is essentially a laboratory phenomenon, it is not an uncommon clinical experience for a physician to administer "God's own medicine" to a patient with bronchial asthma or status asthmaticus only to pronounce the patient dead soon after the injection. The inference one might draw is that morphine when used excessively over a long period causes bronchial spasm, which in turn may produce pathologic pulmonary changes. I believe that the bronchial spasm which may exist clinically can act only as a contributory factor. This opinion is based on my own observations as well as on the fact that few of the addicts were treated for bronchial asthma. Again, while it is true that morphine and the phenanthrene alkaloids produce contraction of smooth muscle in lower animals, repeated injections of the same drugs fail to bring about similar changes [10] in the same animals.

## SUMMARY OF EXPERIMENTAL WORK FORMING THE BASIS OF THESE OBSERVATIONS

Brunelli,[11] in his work on cats, was able to demonstrate that morphine sulfate, when injected in amounts of 10 to 20 mg. per kilogram of body weight into large decerebrated cats under artificial respiration produced a conspicuous fall in blood pressure in the systemic circulation, a fall in pressure in the left auricle, a temporary rise in pressure in the pulmonary artery and an increase in volume of both liver and lungs. When smaller doses of morphine sulfate were injected he obtained some peripheral and splanchnic vasodilatation and a slight increase in pressure in the pulmonary artery. When 20 mg. of morphine sulfate per kilogram of body weight was administered intravenously, an increase in resistance in the lesser circulation and in the liver was noticed. This result, according to Brunelli, was due to a change in the

9. Jackson, C., Jr., in Cushny,[8] p. 257.

10. Cushny,[8] p. 253.

11. Brunelli, B.: L'influenza della morfina sul regime tensivo del grande e del piccolo circulo, Arch. di farmacol. sper. **57**:78 (Feb. 1) 1934.

capillary permeability with the tendency to absorb water. At the same time there was a change in the osmotic pressure of the pulmonary colloids, with absorption of water in the pulmonary veins. Two factors, therefore, were present: (1) with higher doses of morphine sulfate used intravenously, an increase in the capillary permeability and a tendency of the pulmonary colloids to absorb water; (2) a decrease of the osmotic pressure of the blood. Both phenomena produced a shift of a considerable volume of water from the blood into the tissues.

If Brunnelli's laboratory findings are correlated with my clinical observations it becomes understandable why so large a number of addicts displayed increased bronchovascular markings and emphysema of the lungs. Incidentally, Brunelli's work may also explain the frequent appearance of obliteration of the costophrenic sinuses and thickening of the right interlobar fissures in so many (175, or 24.3 per cent) of my cases (table 2). These changes may represent organization of fluid in the free pleural space and in the interlobar fissure which is probably the result of transudation due to altered capillary permeability.

Luisida,[12] working independently of Brunelli, was able to show similar findings. He assumed that morphine sulfate, because of its action on smooth bronchial musculature and the resultant increase in tone, may exert a similar action on the pulmonary veins and thus influence the pulmonary circulation.

By means of oncometric readings, Luisida succeeded in demonstrating, among other changes, the following phenomena: After administration of morphine sulfate in large doses into the veins of cats, a rise of pressure in the pulmonary veins, an increase of pressure in the pulmonary artery and an increase in volume of the lungs were noticed. It was also observed that after the injection of the drug after a considerable period there was a fall in pressure in the pulmonary arteries, originating in the heart and not in the blood vessels. Luisida concluded that in addition to the direct action of the drug on smooth muscle the pulmonary veins are possessed of an important narrowing apparatus which is sensitive to morphine sulfate.

## COMMENT

The problems which are discussed are as follows: the existence of abnormal pulmonary roentgen findings in 86.5 per cent of drug addicts, about 30 per cent of whom showed foci of infection of the upper

12. Luisida, A.: Neue Untersuchungen über die Wirkung des Morphiums auf Blutgefässe, besonders Lungengefässe, Arch. f. exper. Path. u. Pharmakol. **132**:296, 1928.

respiratory tract on routine physical examination; the evaluation of individual factors, such as chronic infections of the upper respiratory tract and diseases not necessarily related to the lungs, and the possible modes of production of the changes described. An attempt is made to establish physiologic principles on which the observations might be based.

I agree with other workers that infections of the upper respiratory tract play an important role in the production of structural changes in the lungs. However, in the present group of cases the maximum number in which there were obvious foci of infection was only 30 per cent. This leaves 70 per cent of cases in which there were abnormal pulmonary findings unexplained by any apparent etiologic factor. Again, it must be conceded that not all persons with foci of infection have diseases of the lungs. The age range itself (average 39 years) tends to rule out such marked pulmonary changes among so many persons. Of the diseases which coexisted or developed during the period of incarceration, only tuberculosis is to be considered. Tuberculosis in all its forms constituted only 7 per cent (table 2).

In the discussion of modes of production of structural changes in the lungs the experimentally produced effects of morphine on smooth muscle are considered. This, as has been mentioned, is not without clinical significance. Finally, the experimental work of Brunelli and Luisida lends strong support to the conception that morphine sulfate when used in large doses over a prolonged period will produce definite structural pulmonary changes as well as alteration in the pulmonary circulation.

## SUMMARY AND CONCLUSIONS

Roentgen examination of the chests of several thousand drug addicts at the Riker's Island Hospital has been made in the past five years; a preponderant number displayed abnormal findings.

During the past fifteen months 674 addicts were studied by means of thoracic roentgenograms.

Over 85 per cent presented abnormal pulmonary findings. The commonest changes observed were those characteristic of hypertrophic emphysema (30.7 per cent). The remainder showed varied pathologic features, i. e., atrophic emphysema (13.94 per cent), increased bronchovascular markings (70.16 per cent), emphysema associated with obliteration of costophrenic sinuses and thickening of the right interlobar fissure (24.13 per cent) and fibroindurative tuberculosis (5.78 per cent).

One hundred patients were examined for infections of the upper respiratory tract. The maximum number of cases in which such foci

could possibly have played a contributory role in the production of the pulmonary abnormalities was 30 per cent.

Eighty addicts were confined in the hospital for a number of different diseases which did not have any bearing on the changes described.

The abnormal pulmonary features were somewhat more pronounced in patients on whom roentgen examination was done during the height of the period of withdrawal. This was probably due to somatic changes.

A summary of the experimental work of Brunelli and Luisida shows conclusively that a definite relation exists between the use of morphine sulfate and pulmonary pathologic changes in lower animals.

# Progress in Internal Medicine

## SYPHILIS

### A REVIEW OF THE RECENT LITERATURE

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The material for this article has been selected from publications which appeared from July 1938 to June 1939. As in previous reviews,[1] it has been necessary to select material rigidly. Little attention has been paid to serologic aspects of the subject, and case reports have been almost wholly eliminated.

### HISTORY OF SYPHILIS

In a charmingly written article, Zimmermann [2] describes epidemics of extragenital syphilis occurring between 1497 and 1624. Most of these epidemics had their origin from cupping in public baths. An outbreak of syphilis occurred in Frankfort on the Main, Germany, in 1496. The city authorities, after consulting with the three city physicians, ordered the keeper of the Red Bath to discharge his "poxed" helper or the bath would be closed. A later epidemic, in Brünn, Czechoslovakia, is described in a treatise by Thomas Jordanus, which was published in 1580. Zimmermann offers his own translation of this treatise. Jordanus describes the suffering of those afflicted as follows:

> Here [the bath outside the Green Gate] the scourge had its origin, here its seeds were conceived. For on that day of winter which astronomers determine by the entrance of the Sun into the Ram, commonly called the feast of St. Lucia [December 13], a fortnight before the Christmas holidays, in the coldest part of the winter of 1577, whosoever entered the stew on this day and had their skin scarified and were cupped, all were said to have been infected. They experienced

Reprints of this article are not available.

From the Syphilis Division of the Medical Clinic, Johns Hopkins University and Hospital.

1. (*a*) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1935. (*b*) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936; (*c*) **60**:887 (Nov.) 1937. (*d*) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **62**:1029 (Dec.) 1938.

2. Zimmermann, E. L.: Extragenital Syphilis as Described in the Early Literature (1497-1624), with Special Reference to Focal Epidemics, Am. J. Syph., Gonor. & Ven. Dis. **22**:757 (Nov.) 1938; **23**:104 (Jan.) 1939.

no harm at once. The symptoms of the disease did not appear immediately. In some, they remained latent for eight days. In others, they remained hidden for two weeks, even for a month, according (as the saying goes) to the strength of the infecting agent or the resistance of the patient. Meanwhile they were oppressed by a strange torpor. They were listless in performing their usual duties and depressed. Neither mind nor hand and foot functioned. They were seen wandering about aimlessly, more like shadows than men. The natural color of their faces had paled, the luster of their eyes had dimmed and dark circles had developed like those seen in menstruating women. Then frank symptoms of the disease manifested themselves. The cupped areas swelled and were invaded by an intense and intractable heat, followed by abscesses and foul ulcers, flowing with sanies and corruption. Scattered about to the extent of the palm of the hand were pustules. The areas were studded with small abscesses, which, upon being opened either with a knife or with topical applications, discharged a thin, serous, foul phlegm. In others, the discharge was corrosive. The flesh surrounding the site of cupping became foul and corroded and gave forth a stench as comes from Telephian and phagedenic ulcers. To begin with, it was astonishing that from so many cups applied (some had about ten, several about three times that number, applied), of all these, only one, or at most two, developed into foul ulcers, with the lone exception of the mother-in-law of Lawrence, the tailor, who had three ulcers develop out of fifteen cups applied. In many the entire body was covered with pustules, the countenance was horrid to look at. The back, chest, abdomen, feet, indeed the entire body from head to toes, were defiled by a scabby itch, with crusted ulcers but slightly raised above the level of the skin, the size of a two kreutzer piece or of a thumb nail, with a red halo and a glistening surface as in the condition called by barbarous authors [Arabians and Arabists] tinea. From these oozes a thick, sluggish mucus. When the scabs drop off and the lesions heal, there are left behind dark spots, of a leaden or brownish color, differing from freckles or vitiligo. As the disease progressed, hard tumors (calli) formed on the scalp, which, upon being ruptured or cut open to the great pain and amid the loud cries of the patient, discharged a honey-like, resinous substance. Following closure of these foul and malignant ulcers, so difficult to cleanse and no less difficult to fill in with new flesh, further symptoms erupted. All the joints of the body, the forearms, the shoulders, the elbows, the arms, the calves, the shins, the feet, were excruciatingly racked with stabbing pains, as if pierced by sharp instruments, as if they were being gashed with knives or burned with hot forceps. . . . Most intense is the pain where the tibia is bare of flesh, uncovered by the bellies of muscles and invested only by periosteum. Their heavy limbs required support. They cannot be sustained or raised through their own strength. Some, indeed, when their paralysis has abated somewhat, must be lifted upon the shoulders of others. There is no rest. There is constant shouting and weeping, groaning over pains which never cease, especially at night when the weary limbs are ordinarily restored by peaceful sleep. They lie awake throughout the night. At dawn a false shadow of peace falls upon them. But their torments recur. If they accuse the day of being hostile and spiteful, they must indeed abhor the image and recollection of night. These nights of anguish were not numbered by one or a few, but lasted a whole month. In vain they crammed themselves with remedies.

The second half of Zimmermann's paper deals with outbreaks of extragenital syphilis as a result of wetnursing and midwifery during the latter half of the sixteenth century. He provides translated paragraphs from treatises by Ambroise Paré, Antonius Brassavolus and the midwife Louise Bourgeois.

Goodman [3] gives some fifty references to the early literature (1500-1900) dealing with syphilis in childhood.

A Pueblo skull, identified as Tuzigoot II-50, found during the excavation of the Tuzigoot ruins near Clarksdale, Ariz., is described by Denninger.[4] Tuzigoot was occupied probably before 1000 A. D. and abandoned shortly after 1350 A. D. The lesions found in the skull are thought to be typical of syphilitic lesions of bone.

### SPIROCHAETA PALLIDA

*Staining.*—Haire [5] describes a new method for staining Spirochaeta pallida. Aqueous stains, because of their high surface tension, penetrate poorly. Alcohol, although of low surface tension, penetrates poorly because it coagulates tissue. The author therefore suggests using hexylresorcinol as a solvent for the dye. In the technic described, a 1 per cent solution of gentian violet in hexylresorcinol is employed. The method as described by the author is simple, but in our hands it has not proved entirely satisfactory.

Garvin [6] and Ono [7] also suggest new staining methods; and Krajian,[8] whose method was first discussed in these reviews in 1936, presents an additional description of it. The clinical application of Krajian's staining technic in a large hospital laboratory is discussed in two papers by Chambers and Scholtz, to be referred to presently.

*Culture.*—Renewed failure in attempts to culture virulent S. pallida are reported by Bessemans and de Meirsman [9] and by Crespel, Delavenne and Huberty.[10] The biologic nature of those strains of spirochetes which can be cultured successfully (all avirulent) is discussed by Koch.[11]

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3. Goodman, H.: Historic Pronouncements on Syphilis in Children, Arch. Pediat. **55**:651 (Oct.) 1938.

4. Denninger, H. S.: Syphilis of Pueblo Skull Before 1350, Arch. Path. **26**: 724 (Sept.) 1938.

5. Haire, R. D.: A Practical Method of Staining Treponema Pallida by Means of Low Surface Tension Stain, J. Lab. & Clin. Med. **23**:1215 (Aug.) 1938.

6. Garvin, T.: Spirochetal Stain on Paraffin Section, Am. J. Clin. Path., Tech. Supp. **2**:144 (July) 1938.

7. Ono, K.: Färbung der Spirochäten im Strichpräparate mittels Kal. Permanganatlösung, Acta dermat. **31**:69, 1938.

8. Krajian, A. A.: A Reliable Method of Staining Spirochaeta Pallida in Smears, Arch. Dermat. & Syph. **38**:427 (Sept.) 1938.

9. Bessemans, A., and de Meirsman, E.: Tentatives de culture de Tréponémia pallidum sur la membrane chorio-allantoïdienne de l'embryon de poulet vivant, Compt. rend. Soc. de biol. **127**:847, 1938.

10. Crespel, C.; Delavenne, E., and Huberty, V.: Sur quelques souches de culture du tréponème de Schaudinn, Arch. Inst. prophylac. **10**:89, 1938.

11. Koch: Zur Biologie der Pallidakultur, Arch. f. Dermat. u. Syph. **177**:216, 1938.

*Dissemination.*—Levaditi, Vaisman and Rousset-Chabaud [12] grafted bits of rabbit testicular syphiloma on the backs of mice, which were killed at intervals of from two to forty-two days. When the inoculated areas were studied histologically, it was found that spirochetes had entered the neighboring lymphatics by the second day; by the forty-second day there was a generalized infection of the lymphatic system. Spirochetes were also present in the walls of the blood vessels [13] in the infected region on the first, third and fifth day after infection, and blood from infected mice was infectious for rabbits on the first, third, twelfth and thirty-fifth days.

### PINTA CAUSED BY ORGANISM MORPHOLOGICALLY IDENTICAL WITH S. PALLIDA

Pinta, a cutaneous disease practically limited to tropical America, has been previously thought to be due to fungus infection. It is an extremely chronic disease, which may attack the skin of the entire body (but not the viscera or nervous system so far as is known) and which shows no tendency to spontaneous cure. A group of workers in Habana, Cuba, headed by Sáenz, has discovered an organism which is morphologically identical with S. pallida (both in dark field and stained preparations) in serum obtained from skin scrapings and lymph nodes. These observers have demonstrated the newly discovered spirochete in 94 per cent of 127 patients examined in Cuba and Mexico; their findings are said [13] to have been confirmed by Pardo-Castello. Moreover, some evidence has been found which suggests that the disease is transmitted by an insect vector (Similium haematopotum). The details of these new studies are supplied in papers by León y Blanco,[14] by Sáenz, Grau Triana and Alfonso Armenteros,[15] by Curbelo and Conde Mateo [16] and by Gonzales Herrejón and Ortiz Lombardini.[17]

12. Levaditi, C.; Vaisman, A., and Rousset-Chabaud, D.: Le mécanisme de la dispersion tréponemique chez les souris atteintes de syphilis expérimentale cliniquement inapparente, Bull. Acad. de méd., Paris **119**:154 (Feb. 1) 1938.

13. Discovery of the Causative Organism of Pinta, editorial, Arch. Dermat. & Syph. **39**:709 (April) 1939.

14. León y Blanco, F.: Sobre un Treponema encontrado en los enfermos de "mal del pinto," Medicina, México **18**:617 (Dec. 25) 1938; Estudios sobre la etiología del "mal de pinto," ibid. **18**:624 (Dec. 25) 1938.

15. Sáenz, B., and Grau Triana, J.: Estado actual del problema de la pinta en Cuba, Rev. de med. y cir. Habana **44**:1 (Jan. 31) 1939. Sáenz, B.; Grau Triana, J., and Alfonso Armenteros, J.: Reseña histórica del "mal del pinto" en nuestro país, Rev. méd. cubana [**50**]:21 (Jan.) 1939.

16. Curbelo, A., and Conde Mateo, E.: Ensayos experimentales sobre el agente causal de la pinta encontrado en Cuba, Rev. méd. cubana [**50**]:25 (Jan.) 1939. Curbelo, A.; Castro Palomano, J.; Conde Mateo, E., and Garzon, L.: Ensayos experimentales sobre et agente causal de la pinta encontrado en Cuba, Rev. de cien. méd. **1**:134 (Oct.) 1938.

*(Footnotes continued on next page)*

EXPERIMENTAL SYPHILIS

*Congenital Syphilis.*—Kemp and Fitzgerald [19] and Takahashi [20] add further experimental evidence to show that congenital syphilis does not occur in mice and rabbits. Indeed, Kemp and Fitzgerald observed no effect on the growth and development of the litters of infected mothers, though Takahashi found a high incidence of abortion and of various dystrophies among the animals which survived. Kemp and Fitzgerald add the further important contribution that there was no evidence of immunity transmitted from infected mothers to healthy offspring, since the latter could be as readily infected with syphilis as could young rabbits from normal mothers.

*Aortic Syphilis in Rabbits.*—Takahashi [21] studied the histopathologic changes of the aortic wall in 168 syphilitic and 50 nonsyphilitic rabbits (among the latter 13 with yaws, 3 with rat bite fever and 34 that were normal). Twenty-nine (17.2 per cent) of the syphilitic animals, and none of the nonsyphilitic group, were found to have lesions in the aorta. Twelve of the syphilitic animals had small saccular aneurysms. The histopathologic picture in 25 aortas was similar to that found in so-called epinephrine sclerosis or in spontaneous arteriosclerosis; in 4 it resembled that seen in syphilitic mesaortitis in man. In 2 instances S. pallida was demonstrated in the aortic wall by successful subscrotal inoculation of normal rabbits, though unfortunately Takahashi does not record the number of unsuccessful attempts.

*Syphilis and Yaws.*—As a contribution to the argument over the identity of syphilis and yaws, Ferris and Turner [22] inoculated animals with three strains each of Spirochaeta pertenuis and S. pallida and

17. Gonzales Herrejón, S.: Resumen histórico de las principales ideas etiológicas respecto al "mal del pinto," Medicina, México **18**:619 (Dec. 25) 1938. Gonzales Herrejón, S., and Oritz Lombardini, M. del C.: ¿Es el Simulium haematopotum (Malloch) transmisor del mal del pinto? ibid. **18**:631 (Dec. 25) 1938.

18. Levaditi, C.; Vaisman, A., and Rousset-Chabaud, D. (Mme.): Mode de dispersion du virus syphilitique dans l'organisme de la souris atteinte de syphilis expérimentale cliniquement inapparente: Rôle de la circulation sanguine, Bull. Acad. de méd., Paris **120**:191 (Oct. 11) 1938.

19. Kemp, J. E., and Fitzgerald, E. M.: Studies in Experimental Congenital Syphilis and the Transference of Immunity from Immune Syphilitic Female Rabbits to Their Offspring, J. Invest. Dermat. **1**:353 (Oct.) 1938.

20. Takahashi, H.: Experimentelle Untersuchungen über die angeborne Syphilis, Jap. J. Exper. Med. **16**:1 (Feb. 20) 1938.

21. Takahashi, H.: Beiträge zur histopathologischen Untersuchung der experimentellen Syphilis und Frambösie bei Kaninchen: Pathologische Veränderungen der Aortenwand, Jap. J. Exper. Med. **15**:321 (Oct. 20) 1937.

22. Ferris, H. W., and Turner, T. B.: Comparison of Cutaneous Lesions Produced in Rabbits by Intracutaneous Inoculation of Spirochetes from Yaws and Syphilis, Arch. Path. **26**:491 (Aug.) 1938.

subsequently studied the gross and microscopic character of the lesions produced. On the whole, and although the cellular reactions were qualitatively identical for lesions of approximately the same size, the lesions of yaws developed more slowly, were smaller, contained fewer spirochetes and involuted more rapidly than the lesions of syphilis.

*Syphilis and Cirrhosis of the Liver.*—When Ferris [23] produced cirrhosis of the liver in syphilitic and control rabbits by chronic chloroform poisoning, the extent of the cirrhosis was approximately the same in both groups, suggesting that in this animal, at least, syphilis plays no part in the production of cirrhosis.

*Effect of Antisyphilitic Drugs on the Sexual Cycle.*—Ogihara [24] observed that when female rats were given bismuth preparations ovulation stopped. Arsphenamine and mercury preparations had no such effect. However, the combination of arsphenamine and a bismuth compound had the same effect as the bismuth compound alone.

*Syphilis in Lower Monkeys.*—There has been some disagreement as to whether lower monkeys could be infected with syphilis. Bessemans, de Wilde and van Thielen [25] have been able to infect 2 of 6 monkeys (Macacus rhesus), using massive inoculums, by scarification of the eyebrow or by scrotal or testicular injection. In none of the animals did clinical evidence of syphilis develop but 1 monkey later had a positive serologic test for syphilis, and in the case of this animal and 1 other it was possible to prove infection by lymph node transfer of the disease to normal rabbits.

*Chemotherapy and Fever.*—Borchers [26] studied experimentally the therapeutic effect of combined fever and chemotherapy. His experiment was carried out on three groups of rabbits: 1. Three syphilitic rabbits were given fever (maximum, 41.7 C. [106 F.]) by the administration of a vaccine (Stimulol, a mixed vaccine) without other treatment. The syphilitic lesions increased in size. 2. Three control animals were given three doses (7 to 8 mg. per kilogram) of neoarsphenamine at forty-eight hour intervals. The lesions healed, but two relapsed, one in thirty-six days, the other in thirty-two days. The third animal died before

23. Ferris, H. W.: Cirrhosis of the Liver in Rabbits with Continued Chloroform Poisoning and with Associated Syphilitic Infection, Arch. Path. **26**:1023 (Nov.) 1938.

24. Ogihara, M.: Experimentelle Studien über den Einfluss der antiluetischen Präparate auf den Sexualzyklus, Mitt. a. d. med. Akad. zu Kioto **23**:713, 1938.

25. Bessemans, A.; de Wilde, H., and van Thielen, E.: Syphilis inapparente du macaque et résistance à la pallidoïdose, Compt. rend. Soc. de biol. **129**:373, 1938.

26. Borchers, G.: Tierexperimentelle Beiträge zur Fiebertherapie den Syphilis, Arch. f. Dermat. u. Syph. **176**:705 (June) 1938.

completion of the experiment. 3. In the third group fever and neoarsphenamine were combined, three doses (8 mg. per kilogram) of neoarsphenamine being given at a time when the body temperature was 41 to 41.7 C. (105.8 to 106 F.). The lesions disappeared promptly in all, and there was one instance of relapse among 4 animals.

While the dose of 8 mg. per kilogram is distinctly subcurative (curative dose of neoarsphenamine, 15 to 25 mg. per kilogram), the author studied the effect of still smaller doses, alone and in combination with fever. When 3 mg. per kilogram of neoarsphenamine was given alone to a syphilitic rabbit, there was no effect on lesions or organisms; when this same dose was combined with fever (41 C.) in 2 animals, motile organisms disappeared from the testicular syphilomas within twenty-four to forty-eight hours.

This is an interesting experimental confirmation of the clinical suggestion of Simpson and Kendell, referred to in last year's review.[1d]

*Artificial Heat.*—Beck [27] infected mice with S. pallida and fifty-eight to four hundred and sixty days after inoculation treated them with artificial fever (produced by hot air). He found that if a rectal temperature of 104 F. or more was maintained continuously for thirteen and a half hours, the organisms disappeared from the brain as well as from other tissues in two thirds of the mice. However, if the mice were treated by a series of short fevers, lasting fifteen minutes at a time, spirochetes disappeared in only one fourth of the animals.

For many years those familiar with experimental syphilis in the rabbit have known that in the heat of summer the incubation period of syphilis in that animal is prolonged, local lesions are inconspicuous, and generalized lesions of syphilis are absent. In modern syphilis laboratories, therefore, the animal rooms are air conditioned. Chorazak,[28] apparently not aware of this fact, attempts to explain the summer phenomenon of syphilis in rabbits on the basis of dietary change. By varying the vitamin content of the diet he found that when an abundance of vitamin $B_1$ was fed the incubation period of syphilitic lesions was prolonged. An excess of vitamins A and D appeared to shorten the incubation period. The experiment is interesting in the light of the clinical improvement said to occur occasionally in tabes dorsalis when vitamin $B_1$ is administered.[29]

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27. Beck, A.: The Influence of Artificially Induced Fever upon Syphilitic Infection of Mice, Brit. J. Ven. Dis. **14**:221 (July) 1938.

28. Chorazak, T.: Der Einfluss der Vitamine auf die Entwicklung der syphilitischen Impfveränderungen in der experimentellen Kaninchensyphilis, Bull. internat. Acad. polon. d. sc. et d. lett., Cl. méd. **214**:219 (Feb.) 1938.

29. Metildi, P. F.: The Treatment of Tabetic Lightning Pains with Thiamin Chloride: Preliminary Report, Am. J. Syph., Gonor. & Ven. Dis. **23**:1 (Jan.) 1939.

*Effect of Hibernation on Syphilis.*—Bessemans, de Wilde and de Moor [30] have confirmed the work of Jahnel,[31] who demonstrated that the rell-mouse (a hibernating animal) if inoculated with S. pallida prior to hibernation is free of syphilitic infection after the hibernating period. Jahnel believed that the disappearance of the syphilitic infection was due to an immune humoral response rather than to a lowering of body temperature. Bessemans and collaborators were able to produce syphilitic infection in the hedgehog and hamster and noted that after hibernation lymph node transfers from these animals gave negative results. Node transfers from control animals kept in a warm environment to prevent hibernation gave consistently positive results. Artificial hibernation brought about by placing the hamster and hedgehog in a refrigerator for a period of twenty days resulted in disappearance of the syphilitic infection.

*Immunity.*—In one of the most important papers of the year, Turner [32] has clearly demonstrated that immunity in syphilitic rabbits is at least partly humoral. By a series of appropriate experiments he has shown that when an emulsion containing virulent S. pallida is added to serums from normal rabbits and from untreated immune syphilitic rabbits infected with a homologous strain of S. pallida and the mixtures after incubation at 37 C. are injected intracutaneously into normal rabbits, typical syphilitic lesions commonly develop at the sites of inoculation of the normal serum–spirochete mixture, while at the sites of inoculation of immune serum–spirochete mixtures, usually either no lesions develop or the incubation period of the resulting lesions is shorter and the lesions remain smaller than those produced by normal serum–spirochete mixtures.

In a series of preliminary experiments, of 56 areas inoculated with syphilitic serum–spirochete mixtures, the suppressive action of the syphilitic serum was manifest in 42; in 10 areas questionable evidence of protection was noted, and in 4 areas there was no evidence that the syphilitic serum had exerted a suppressive or protective action.

The results of the protection test in three other series of experiments were as follows: 1. Of 12 areas in 6 rabbits inoculated with normal serum–spirochete mixtures, typical syphilitic lesions developed in all, while in the same number of areas inoculated with immune serum–

30. Bessemans, A.; de Wilde, H., and de Moor, A.: Effet du sommeil hibernal sur la syphilis du hamster et du hérisson, Compt. rend. Soc. de biol. **129**:376, 1938.

31. Jahnel, F.: Ueber den Einfluss des Winterschlafes auf die Syphilisspirochäten in Gehirn und den inneren Organen des Siebenschläfers: Ein Beitrag zur Frage der Selbstheilung bei der tierexperimentellen Syphilis, Arch. f. Dermat. u. Syph. **171**:187, 1935.

32. Turner, T. B.: Protective Antibodies in the Serum of Syphilitic Rabbits, J. Exper. Med. **69**:867 (June) 1939.

spirochete mixtures there was complete or partial suppression of lesions in all. 2. Of 45 areas inoculated with spirochetes plus serum from 10 different immune syphilitic rabbits, definite evidence of protection was observed in 37, questionable evidence in 5 and no evidence of protection in 3. 3. In 8 areas in 4 rabbits inoculated with immune serum–spirochete mixtures, no lesions developed during the period of observation, while in each of 8 areas in the same rabbits inoculated with one of two normal serum–spirochete mixtures typical syphilitic lesions developed.

From these experiments Turner concludes, therefore, that during the course of syphilitic infection in rabbits specific humoral antibodies develop which can be demonstrated by an appropriate "protection test." The presence of these antibodies is associated with a high degree of acquired immunity to the disease.

Chesney, as a part of his important work on immunity in syphilis, has studied with Woods and Campbell,[33] the extent to which the eye participates in the general resistance which develops in rabbits during syphilitic infection. Forty-three treated immune animals were inoculated with the homologous strain of S. pallida, the inoculum being introduced either into the cornea or into the anterior chamber. Forty-one normal animals were used as controls. Of the immune animals, 27 (62 per cent) showed lesions in the cornea; of the controls, 90 per cent developed corneal lesions. The authors continue:

> The lesions developing in the corneas of the "immune" animals had a longer incubation period on the average, were often of longer duration, and in some instances were more severe than the lesions developing in the control animals. In the case of some animals, also, they showed a greater tendency to recur. . . .
>
> It is concluded that the eye of the syphilitic rabbit does not share to the same extent as other tissues in the general resistant state which develops in that animal during the course of syphilitic infection.

In their discussion of these results, the authors say:

> The results of these experiments offer a possible explanation for the well established clinical observation that the interstitial keratitis of congenital syphilis is prone to recur in patients with that condition. . . . one might infer that this tendency to recur is due to failure of the cornea of the patient with congenital syphilis to participate in the general defense reaction against the infection. Such an inference would suffice to explain the tendency of such patients to show repeated relapses of interstitial keratitis, but would not explain the fact that this condition is singularly resistant to antisyphilitic treatment. Some ophthalmologists, notably Igersheimer and Derby, have sought to explain the proneness of interstitial keratitis to relapse on the basis of allergy . . . The experiments reported in this communication lend no support to this view. Furthermore, attempts made by us to

33. Chesney, A. M.; Woods, A. C., and Campbell, A. D.: Observation on the Relation of the Eye to Immunity in Experimental Syphilis, J. Exper. Med. **69**:163 (Jan.) 1939.

sensitize the corneas of normal rabbits to *T. pallidum* by the preliminary injection of killed suspensions of that organism were entirely fruitless . . . there is no direct evidence that such [allergy] is the case, . . .

## SERODIAGNOSIS OF SYPHILIS

As in previous years, it is impossible, because of limitations of space, to refer to the large volume of technical papers dealing with the serodiagnosis of syphilis. Only a few of those which present details of practical importance to the clinician can be mentioned.

In October 1938 there was held an assembly of laboratory directors and serologists under the auspices of the Committee on Evaluation of Serodiagnostic Tests for Syphilis and the United States Public Health Service, at which seventeen papers (later published as a symposium [34]) were presented and certain recommendations adopted. Among the essayists were Parran, Eagle, Hinton, Kahn, Kline, Kolmer, Mahoney and Harrison, Hazen, Senear, Moore, Perry, Hoyt, Casselman, Sanford, Whittemore, Giordano, Wadsworth and Lamb; the discussants included, among others, Godfrey, Lange, Nelson, Sherwood and Stokes.

The symposium dealt with four topics: (1) the need for adherence to conventional technics in the reliable routine performance of serologic tests for syphilis; (2) improvement of methods for determining the efficiency of the performance of serologic tests; (3) training of laboratory personnel, and (4) the desirability of state departments of health approving or licensing laboratories for the performance of serodiagnostic tests for syphilis. There were also descriptions and demonstrations by Eagle, Hinton, Kahn, Kline and Kolmer of the latest developments in their several technics.

*Need for Adherence to Conventional Technics.*—In the recommendations of the committee on this topic appears the following:

> [There is] great variation in the results obtained in various State, hospital and private laboratories. . . . The poorest results were usually obtained when there was considerable divergence from the technic described by the originator of a method. . . . Experience has shown . . . that modifications which involve considerable divergence from the conventional technic described by the originator should not be attempted except as a research project in laboratories adequately equipped with personnel and material for the conduct of such investigations.

*Improvement of Methods for Determining the Efficiency of the Performance of Serologic Tests.*—After the presentation of six pertinent papers on this topic, the committee concluded that a system of checks of serologic performance should be set up in each state, with a laboratory of proved efficiency (state health department or other) setting a standard of specificity and sensitivity in performance against

34. The Serodiagnosis of Syphilis, Ven. Dis. Inform., 1939, supp. 9.

which participating laboratories might measure their own results. *To qualify as satisfactory, a laboratory should attain a sensitivity rating not more than 10 per cent below that of the control laboratory and a specificity rating of not less than 99 per cent.* (The italics are ours.)

These recommendations should be widely publicized and should be familiar to clinicians as well as to laboratory directors. Even yet there is too little clinical appreciation of the fact that serodiagnostic tests for syphilis are not exactly standardized or standardizable procedures and that, in order to avoid diagnosing syphilis in noninfected persons or missing the disease in those who are infected, the clinician should know not only what technic the laboratory of his choice employs but also how efficient that laboratory is when checked against known good performance.

In order to simplify the interpretation of serologic results by clinicians, the committee also repeated and emphasized the recommendation repeatedly stressed by three League of Nations serologic conferences, beginning in 1923:

*"Qualitative serodiagnostic tests should be reported as positive, doubtful, or negative"* (the italics are ours), and the confusing system of plus marks so commonly employed should be abandoned.

It was also emphasized by one of the essayists (Moore) that

> the quantitative serologic test, by whatever method quantitation is carried out, has absolutely no diagnostic value whatever for the . . . practitioner, and as yet it has comparatively little for the expert . . . At present . . . the value of the quantitative serologic test lies in the research rather than in the practical field.

In the discussion there was general agreement as to the recommendation that tests be reported as positive, doubtful and negative, except from Kolmer, who wished to divide the term "positive" into "strongly positive" and "weakly positive" and who has subsequently defended his stand in a separate paper.[35] It was pointed out, however, that this adoption of terms was, in effect, a retention of the obsolete system of plus marks and an attempt at rough (wholly valueless) quantitation. If the serologist means by the term "weakly positive" that he thinks the patient probably has syphilis, the word "weakly" is superfluous. If, on the other hand, the serologist is dubious as to the interpretation of a weakly positive result, a better term is "doubtful," a word which deliberately interjects into the clinician's mind the meaning the serologist intends to convey.

The discussion of the value of quantitative tests in diagnosis was especially pertinent because of the adoption by the New York State

35. Kolmer, J. A.: Concerning the Method Proposed for Reporting the Serological Reactions for Syphilis as Positive, Doubtful and Negative, Am. J. Clin. Path. **9**:121 (March) 1939.

Department of Health Laboratory of an esoteric quantitative technic for routine diagnostic purposes (Wadsworth, Maltaner and Maltaner;[36] Maltaner[37]). This technic differs from the quantitative technics used in most laboratories at the present time in two respects: (1) complement is titered against a fixed amount of serum rather than serum being titered against a fixed amount of complement, and (2) the results are reported in terms of units calculated from the following ratio:

$$\frac{\text{Amount of complement required for 50 per cent hemolysis with serum and antigen}}{\text{Amount of complement required for 50 per cent hemolysis with serum alone}}$$

Discussion of the complex technical details of the quantitation of the Maltaner technic, of the value of this procedure as compared with direct quantitation of serum reagin or of the probable error introduced by the varying anticomplementary activity of different serums is here purposely avoided. Not only is the test itself complicated and unsuited for general performance, but the manner of reporting the results to the clinician is equally complicated and subject to gross misinterpretation, as may be seen from the following paragraph which appears on the reverse of the New York State serologic report blank:

> The quantitative complement fixation test for syphilis permits reporting a numerical value which is a direct index of the degree, or titer, of the reaction. When no reaction occurs, i. e., when the fixation is the same in the test and control, the numerical value of the titer is 1; when the fixation is twice as great in the test as in the control, the titer is 2, etc. A titer of 1.5 has been observed with an extremely small percentage of specimens from healthy individuals. Titers of less than 1.5 have been recorded in the known cases of syphilis when intensively treated, although in some such cases titers of 2 or more may occur occasionally. Whether or not titers slightly in excess of 2 occur in conditions other than syphilis is not known, and therefore the significance of reactions of this degree should be carefully considered. *As a rule, the higher the titer the greater its significance in diagnosis.* [The italics are ours. The italicized statement has no present basis in fact.] Specimens with titers greater than 6 have given reactions of complete fixation (4+) with the previous method. Titers of 100 or greater have been determined in a few cases under special investigation, but it is not practicable at the present time to report the degree of reactions when the titers are greater than 10.

*Training of Personnel and Licensing of Laboratories.*—The papers dealing with these points and the discussion at the assembly of laboratory directors are of greater public health than of general medical interest and will be omitted here.

36. Wadsworth, A.; Maltaner, F., and Maltaner, E.: Quantitative Studies of the Complement-Fixation Reaction with Syphilitic Serum and Tissue Extract: Technic of the Practical Quantitative Test, J. Immunol. **35**:217 (Sept.) 1938.

37. Maltaner, E.: Serologic Tests in the Diagnosis of Syphilis, Am. J. Pub. Health **29**:104 (Feb.) 1939.

*"Presumptive," "Exclusion" and "Screen" Tests.*—An editorial commentator in *The Journal of the American Medical Association* writes as follows: [38]

An increasing widespread use is apparent of tests for syphilis said to be so sensitive that a negative result "excludes" syphilitic infection while a positive result is "presumptive" evidence of syphilis. Confirmation by a less sensitive and more specific procedure is, of course, necessary before such tests can be considered of diagnostic significance. Several aspects of these tests should give pause to serologists and physicians alike, for they promise to cause serious errors, both of omission and of commission, in the diagnosis and treatment of syphilis.

The first criticism concerns nomenclature. Not merely does no laboratory test yet devised "exclude" syphilis, but no laboratory test even excludes the presence of serum reagin. Moreover, it is not necessarily true that a serum giving a negative Kline exclusion or Kahn presumptive result will be negative by every other technic used. In any extended series of tests, certain syphilitic serums are detected only by an ordinarily less sensitive procedure. These paradoxic results are particularly common when both a flocculation and a complement fixation test are used. Finally, the flocculation phenomenon is peculiarly susceptible to zone reactions, i. e. false negative results caused by the presence of excessive amounts of reagin. A serum may be negative with any flocculation test, screen tests included, when tested as whole serum, yet the complement fixation test may be clearly positive and the flocculation procedure may be similarily positive if the serum is tested in 1:10 or 1:20 dilutions. For these several reasons it is clear that the term "exclusion" test is misleading. It would seem preferable to call these procedures "screen" tests, for such they are, and thus to avoid the present confusing terminology.

A far more important criticism applies not to the tests but to the manner in which they are used. Certainly it was not the intention of their originators that these tests were to be used as diagnostic measures; yet reports as difficult to evaluate as "exclusion test positive, diagnostic test doubtful," presented without explanation to the physician, invite the possibly mistaken diagnosis of syphilis. In the hands of experts these exclusion procedures may be highly specific. In the average laboratory they are often not specific, and experience has shown a general average of false positive reactions ranging from 1 to 10 per cent. When a laboratory obtains a positive "exclusion" or "presumptive" result, the burden of proof rests on the laboratory that such a result is not due to laboratory error but reflects the actual presence of reagin.

Indeed, one might properly insist that the clinician be not informed of the result of a hypersensitive screen test unless it is negative, for the weeding out of negative serums is its only proper function. No matter what result is obtained when a positive or doubtful screen test is checked by one or more specific diagnostic tests, only the latter should be reported by the laboratory, and the result of the "exclusion" or "presumptive" test should be withheld. The objection may be raised that a report "exclusion test positive, diagnostic test negative" is a valuable guide to treatment in cases of known syphilis and that such a result indicates the persistent presence of traces of reagin. That point of view is debatable. To the extent that the "exclusion" test may be false, it may be as much in error with syphilitic serums as with nonsyphilitic serums. More important, antisyphilitic treatment is not directed against the presence of serum reagin; it

38. "Presumptive," "Exclusion" and "Screen" Tests for the Serodiagnosis of Syphilis, editorial, J. A. M. A. **112**:541 (Feb. 11) 1939.

is directed against the spirochete. The modern treatment of syphilis properly pays little heed to the serologic response and more to the patient.

Used solely as an intralaboratory procedure to facilitate the recognition of negative serums, the hypersensitive screen test may fill a useful function; but to report positive or doubtful screen tests to the physician as quasidiagnostic tests which he must weigh and interpret cannot fail but cause confusion and invite the mistaken diagnosis of syphilis.

*Provocative Test.*—Barnett, Kulchar and Jones [39] attempt to show that the so-called provocative effect following the injection of neoarsphenamine is an unreliable aid to the diagnosis of syphilis. In an earlier paper [40] the authors describe a method, using the Kline diagnostic test, for the detection of reagin in normal serum. They employed the same technic to determine the provocative effect of neoarsphenamine, 0.45 Gm., in normal and syphilitic persons. Thirty-two normal persons were tested, none of whose serums contained more than 1 unit of reagin (by the quantitative measuring device of the authors) before neoarsphenamine was given. After twenty-four hours the reagin content had increased to 2 units or more in all but 5; in forty-eight hours all but 1 serum showed an appreciable increase in reagin, and in ninety-six hours even this serum had a reagin titer of 3 units. The same procedure was carried out on serums from 30 patients who were being treated for syphilis. Nine of the serums showed no increase in reagin titer. The mean increase in the reagin content of the serums of the nonsyphilitic group was 1 unit; the mean increase in the syphilitic group was 1.3 units. The authors conclude:

. . . since the injection of neoarsphenamine produces an increase in reagin-like substance in nonsyphilitic sera, the provocative reaction is an unreliable procedure and a positive reaction should not be considered diagnostic of syphilis.

*Biologic False Positive Serologic Reactions in the Presence of Infectious Mononucleosis, Respiratory Infections, Relapsing Fever, Tuberculosis and Malaria.*—In the early years of the Wassermann test many diseases other than syphilis were said to give occasionally or often biologic false positive serologic reactions. Later, for two decades or more these statements were discounted except in regard to yaws, leprosy and perhaps malaria. Still more recently evidence is accumulating which indicates that the early opinion was correct and that conditions other than syphilis may provide false positive results.

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39. Barnett, C. W.; Kulchar, G. V., and Jones, R. B.: Quantitative Provocative Reactions in Normal and Syphilitic Sera Following the Injection of Neoarsphenamine, Am. J. Syph., Gonor. & Ven. Dis. **22**:712 (Nov.) 1938.

40. Barnett, C. W.; Jones, R. B., and Kulchar, G. V.: Measurement of Reagin in Nonsyphilitic Sera, Proc. Soc. Exper. Biol. & Med. **33**:214 (Nov.) 1935.

Bernstein [41] found that transitorily positive complement fixation or flocculation or both developed in 6 of 37 personally observed cases of infectious mononucleosis, and Sadusk [42] observed the same phenomenon in 3 of 37 cases of this disease.

Krag and Lønberg [43] point out that when the specificity of a given serologic test is under determination, generally by the selection of samples of serum from a group known to be syphilitic and a group that is nonsyphilitic, the test proves to be remarkably specific, but that when it is put into routine use, with all types of disease being encountered, nonspecificity is often revealed. Of 120,000 specimens of serum from nonsyphilitic patients which were tested in the Danish Serum Institute over a period of eighteen months, 53 (0.04 per cent) gave biologic false positive results. Of the 53 serums giving false positive results, 60 per cent were from patients with respiratory infections. As causes of these false positive reactions the following diseases are listed: pneumonia 14, bronchitis 6, pleurisy 1, pulmonary tuberculosis 2, sore throat 3, otitis media 2, common cold 1, emphysema 1, herpes genitalis 5, rat bite fever 2, malaria 1, gonorrheal pelvic disease 5, torqued uterine fibroma (?) 1, unidentified disease 9.

Chung and Chang [44] found that 7.95 per cent of 88 patients with relapsing fever had biologic false positive blood tests for syphilis. The cerebrospinal fluid of 16 of these patients was examined from two to four times, and that of 9 gave a positive Wassermann reaction; within one to three weeks after the temperature of these 9 patients became normal, the reaction of their spinal fluid reverted to negative. Murrell [45] reports a case of relapsing fever in which the serologic test for syphilis was positive. The patient was given four doses of mapharsen (hemi-alcoholate of 3-amino-4-hydroxyphenylarsine oxide hydrochloride), which cured the relapsing fever, and the serologic tests promptly became negative and remained so.

Parran and Emerson [46] analyzed the serologic results reported for 450 nonsyphilitic patients with pulmonary tuberculosis. All the serums

41. Bernstein, A.: False Positive Wassermann Reactions in Infectious Mononucleosis, Am. J. M. Sc. **196**:79 (July) 1938.

42. Sadusk, J. F.: Temporarily Positive Kahn and Wassermann Reactions in Infectious Mononucleosis, J. A. M. A. **112**:1682 (April 29) 1939.

43. Krag, P., and Lønberg, A.: The Occurrence of Strong Non-Specific Wassermann-Kahn Reactions, Acta dermat.-venereol. **19**:612 (Dec.) 1938.

44. Chung, H. L., and Chang, F. C.: Relapsing Fever: Clinical and Statistical Study of Three Hundred and Thirty-Seven Cases, Chinese M. J. **55**:6 (Jan.) 1939.

45. Murrell, T. W.: Positive Wassermann Reaction in Spirochetal Infections Other Than Syphilis, Arch. Dermat. & Syph. **39**:667 (April) 1939.

46. Parran, T., and Emerson, K.: The Effect of Tuberculosis on Serologic Reactions for Syphilis, Am. Rev. Tuberc. **39**:1 (Jan.) 1939; Ven. Dis. Inform. **20**:1 (Jan.) 1939.

were tested with the Eagle macroflocculation test, the Kline, Kahn and Hinton flocculation tests, and the Kolmer and the Eagle complement fixation tests. Positive or doubtful results were reported with from one to three of these tests for 26 (7.8 per cent) of the 450 patients; none of the 26 gave doubtful or positive results with more than three of the tests employed. The authors conclude:

> . . . inasmuch as with the present serologic tests for syphilis both typical and atypical false doubtful and false positive results are found in serums from tuberculous donors, it is evident that tuberculous toxemia may contribute a confusing factor to syphilis serology. It should not, however, present a major problem in the clinical interpretation of results obtained with carefully conducted serodiagnostic procedures.

Kitchen, Webb and Kupper [47] inoculated 30 nonsyphilitic persons with malaria. Specimens of blood were collected before inoculation, during the incubation period, during paroxysms and for a considerable period after the termination of the malaria. Each patient in whom malaria developed showed a positive serologic reaction for syphilis at some time between inoculation and a date fourteen days after the termination of the attack. In 72 per cent of the cases the positive reaction first appeared during the third and fourth week after inoculation. Positive reactions were observed in a few instances before clinical symptoms of malaria developed. In 68 per cent of the cases the positive reactions appeared during the first two weeks of the febrile period. The percentage of positive reactions was highest during the period from fifteen to twenty-one days after the last paroxysm. The duration of the positive serologic reactions exceeded three weeks in 60 per cent and four weeks in 48 per cent of the cases. This work confirms the work of Ester,[48] who found that in 9 of 10 cases of inoculation with malarial parasites serologic tests for syphilis became positive.

*False Positive Reactions of Cerebrospinal Fluid in Tests for Syphilis.*—McLean and Munger [49] report 10 cases in which cerebrospinal fluid gave biologic false positive reactions in tests for syphilis. The diagnoses in these cases were as follows: encephalomalacic atrophy, encephalomalacia, streptococcic septicemia, electrical burn, extrathecal panniculitis, cerebrospinal rhinorrhea, skull fracture, concussion, neuritis and multiple

47. Kitchen, S. F.; Webb, E. L., and Kupper, W. H.: The Influence of Malarial Infection on the Wassermann and Kahn Reactions, J.A.M.A. **112**:1443 (April 15) 1939.

48. Ester, F.: Sul comportamento di alcune sieroreazioni della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, Gior. di batteriol. e immunol. **17**:502 (Oct.) 1936.

49. McLean, A. J., and Munger, I. C., Jr.: False Positive Wassermanns in Cerebrospinal Fluid, West. J. Surg. **46**:455 (Sept.) 1938.

sclerosis. These authors experimentally produced a positive Wassermann reaction in the cerebrospinal fluid of a dog by injecting intracisternally the fluid from a craniopharyngioma.

Positive reactions of spinal fluid in tests for syphilis have been reported in the past for patients who had spontaneous malaria. Kuske [50] investigated the frequency with which complement fixation tests for syphilis with cerebrospinal fluid from patients being given malaria treatment for gonorrhea became positive. He was unable to demonstrate positive reactions of the spinal fluid from any of these patients. He also noted that positive Wassermann reactions did not develop in the spinal fluid of patients with latent syphilis during malarial infection.

## PUBLIC HEALTH ASPECTS

*Probability of Acquiring Syphilis and Frequency of a Disastrous Outcome.*—In an important paper Vonderlehr and Usilton [51] present the

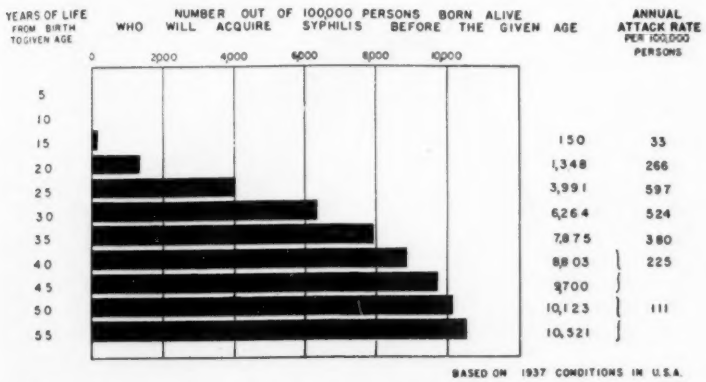


Fig. 1.—Schema showing that the number of persons acquiring syphilis during life is 1 in every 10 (after Vonderlehr and Usilton [51]).

statistical data which justify the statement that "syphilis strikes one out of every ten adults."

> This statement is based on the annual attack rate [based on those found in surveys of licensed treatment sources within the past two years] applied to 100,000 individuals born alive and followed throughout life. Although the annual attack rate seems low, when cumulated so as to indicate the probability of acquiring syphilis by a given age, it is found that 10,000 people before the attainment

50. Kuske, H.: Zur Beurteilung der Luesreaktionen im Serum und im Liquor cerebrospinalis bei Impfmalaria, Dermat. Ztschr. **78**:137 (Aug.) 1938.

51. Vonderlehr, R. A., and Usilton, L. J.: Chance of Acquiring Syphilis and the Frequency of Its Disastrous Outcome, New York State J. Med. **38**:1376 (Nov. 1) 1938; Ven. Dis. Inform. **19**:396 (Nov.) 1938.

of the fiftieth year of life will have acquired syphilis out of every 100,000 born alive.

This rate is different from that found on routine serologic examination of persons tested under the antenuptial physical examination laws, in industry, or in any random sample of the population. Several reasons for these differences are given: (a) Many persons in a random sample are still in danger of acquiring the infection; (b) The blood test for syphilis becomes negative either spontaneously or as the result of treatment in many infected persons; (*a*) Death removes from the population a high proportion of those who are infected.

As to a disastrous outcome of syphilis, Vonderlehr and Usilton present data to show that treatment decreases this probability, especially as to cardiovascular and neurosyphilis, and (an observation important

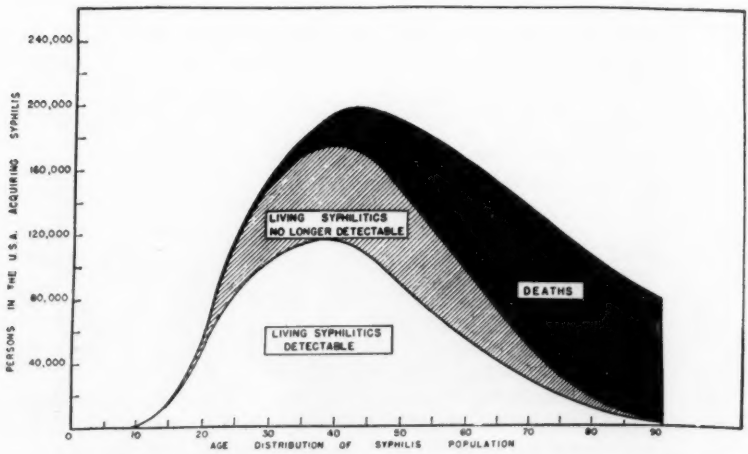


Fig. 2.—Schema showing factors which reduce the number of persons with detectable syphilis to 1 in 100 (after Vonderlehr and Usilton [51]).

to public health officer and clinician alike) that a satisfactory result from the treatment of early syphilis which has been maintained for from three to ten years after treatment is practically certain to be maintained further over a ten to twenty year period.

*Syphilis Control in the South.*—Vonderlehr [52] calls attention to the magnitude of the problem of syphilis in the southern half of the United States and the relative lack of clinics and clinical equipment. Of the 518,000 persons estimated to acquire syphilis annually, 65 per cent are in sixteen southern states and the District of Columbia, though only 30 per cent of the population lives in this area. The medical facilities

52. Vonderlehr, R. A.: The Control of Syphilis in the Southern States, South. M. J. **31**:863 (Aug.) 1938.

so far available in these southern states provide for only about 20 per cent of the medical care needed for the effective control of syphilis. In contrast to this gloomy picture, Sharp [53] describes progress in the South. Eleven of these sixteen states now have full time officers for the control of venereal disease. Ten states distribute antisyphilitic drugs free to the indigent, and two of these states distribute drugs to all patients. In twelve states laboratory facilities for direct and indirect dark field examination are now available. In all states but one, free serologic tests are performed. Efforts are being made to increase epidemiologic investigation and to train health officers, public health nurses, venereal disease control officers and cooperating clinicians.

*Syphilis Control in the City of New York.*—Rice,[54] commissioner of health of the city of New York, discusses the problem of syphilis control in general and outlines the basic principles followed by the New York City Health Department:

> The chief elements of the program are:
>
> 1. Case finding activities to include
>
> (*a*) Popular education.
>
> (*b*) Epidemiological investigation.
>
> 2. Easily available diagnostic services for the general population.
> 3. Treatment services for low income group.
> 4. Follow-up services to retain patients under treatment at least until they are noninfectious.
> 5. Professional education both for practicing physicians and for undergraduate medical students.
> 6. Facilities to aid private physicians and clinics in keeping patients under their treatment including
>
> (*a*) Consultation service,
>
> (*b*) Free drugs,
>
> (*c*) Follow-up service.

*Syphilis in Colleges.*—Tumbleson and Ennes [55] investigated the incidence of syphilis in the colleges of the United States by sending questionnaires to the administrative heads of various institutions. Serologic reports were obtained on 83,000 students. Among white students the rate of positive tests was 2.03 per thousand for men and 1.78 per thousand for women. The rate for Negro students was 26 per thousand

53. Sharp, W. K., Jr.: Progress in Syphilis Control in the Southern States, South. M. J. **31**:866 (Aug.) 1938.

54. Rice, J. L.: Syphilis and Gonorrhea as Public Health Problems, Ann. Int. Med. **12**:503 (Oct.) 1938.

55. Tumbleson, R. C., and Ennes, H. W., Jr.: A Study of Syphilis in American Colleges, J. Social Hyg. **25**:184 (April) 1939.

for men and 27.6 per thousand for women. There was no significant difference among colleges in various regions of the country.

*Epidemiology of Syphilis.*—Smith and Sheppe [56] found a 75 per cent incidence of syphilitic infection among persons who had been in sexual contact with patients suffering from early syphilis.

Clark [57] insists that before syphilis can be eradicated a concentrated effort must be directed toward the reservoirs of infection. One hundred and twenty-two patients with early syphilis named 168 persons with whom they had been in sexual contact, of whom 112 (66.8 per cent) were examined. Of these, 63 (56.2 per cent) were found also to have early syphilis. Among 368 family contacts of the 122 patients, 271 (73.5 per cent) were examined and 37 (13.6 per cent) were found to have early syphilis.

Kulchar and Ninnis [58] determined the source of infection of 1,152 syphilitic patients in San Francisco. Of 909 infected men, 39.8 per cent were infected through contact with prostitutes, 51.1 per cent through clandestine sexual contacts, 4.7 per cent through marital contact and 4.4 per cent through homosexuality. Of 243 infected women, 18.1 per cent were infected through prostitution, 54.3 per cent through clandestine sexual contact and 27.6 per cent through marital contact. The authors feel that from the public health standpoint clandestine sources of infection are relatively more important than prostitution inasmuch as 35 per cent of the prostitutes could be located and put under treatment, whereas only 14 per cent of the clandestine contacts could be traced.

*Cost of Caring for Syphilis.*—Brumfield [59] has estimated the cost of caring for syphilitic persons in Buffalo in 1936. The population of Buffalo is 573,076, of whom 13,563 are Negroes.

> . . . The cost of syphilis . . . (exclusive of the hospitalization of early and latent hospital cases) was $165,352.21 ($0.287 per capita), of which $105,216.21 ($0.183 per capita) was spent for the hospitalization of patients suffering from late manifestations of the disease.
>
> The cost of operating ambulatory clinics was $32,834.52 ($0.058 per capita) and of serologic laboratories $25,274.90 ($0.044 per capita). The cost of antisyphilitic drugs was $1,926.58 ($0.003 per capita.) . . .
>
> A great saving in public funds could be accomplished . . . through case-finding procedures directed toward the placing of patients under treatment in the

56. Smith, D. C., and Sheppe, W. M.: Studies in the Transmission of Syphilis, West Virginia M. J. **34**:101 (March) 1938.

57. Clark, E. G.: Fundamentals in the Eradication of Syphilis, South. M. J. **32**: 460 (May) 1939.

58. Kulchar, G. V., and Ninnis, E. I.: Sources of Infection in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **22**:584 (Sept.) 1938.

59. Brumfield, W. A.: Hospital, Clinic and Laboratory Costs of Syphilis in Buffalo, New York, with a Comparison of Similar Costs in Baltimore, Maryland, Ven. Dis. Inform. **20**:63 (March) 1939.

early stages of the disease and thus preventing late manifestations. The expenditure of funds for such procedures would undoubtedly be saved many times over.

From a compilation of various statistical data, Rice [60] concludes that blindness is due to syphilis in about 15 per cent of cases in this country. Usually it is from primary atrophy of the optic nerve. Since the 1930 census enumerated 63,489 blind persons in the United States, there are about 10,000 persons who are blind because of syphilis. Rice estimates that syphilitic blindness alone causes an annual loss of earnings of $6,000,000 and necessitates special appropriations by taxing bodies and private charity of more than $4,000,000 additional.

*Syphilis and Life Insurance.*—Murrell and Manson [61] properly object to the present approach of insurance companies to syphilis among applicants, i. e., to the question "Have you ever had syphilis?" Those who admit that they have had the disease are either rejected or must pay an augmented premium; those who deny infection present a possible risk which the company ignores. About 2 per cent of applicants for life insurance have syphilis, but only 0.127 per cent admit that syphilitic infection is present. Those persons who admit that they are infected are given undue publicity. The information not only goes through the hands of many secretaries but is then sent to a central bureau. The authors suggest the following remedy:

> (1) Delete the question ["have you ever had syphilis?"] from the blank and go on in entire ignorance. This would not be bad, since at present the companies must be 85 per cent ignorant.
>
> (2) Delete the question and do a routine Wassermann or precipitation test on all applicants for insurance over a certain amount. This would be a complete solution, for a positive serum test is not necessarily proof of the existence of syphilis and is not, therefore, actionable before the courts and its recording would be ethical.

*Laws and Syphilis.*—During the past year there has been much debate, in state legislatures and among physicians, as to laws requiring premarital and prepartum blood tests. Snow [62] is of the opinion that such laws are useful but must not be introduced too quickly. As of March 1939, ten states required premarital serologic tests, and like bills were pending in the legislatures of thirty-three others. Four states required prepartum serologic tests, and like bills were before the legisla-

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60. Rice, E. E.: Cost and Loss from Syphilitic Blindness in the United States, Ven. Dis. Inform. **20**:91 (April) 1939.

61. Murrell, T. W., and Manson, R. C.: Syphilis and Life Insurance, South. M. J. **32**:322 (March) 1939.

62. Snow, W. F.: Protection of Marriage and Childlife Against Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **23**:277 (May) 1939.

tures of eighteen others. Nelson,[63] however, objects to compulsory premarital examination. Stokes and Ingraham [64] take a neutral stand.

An editorial [65] commentator briefly summarizes the arguments in favor of and against premarital laws. The arguments in favor are as follows:

1. They are valuable methods of case finding, the first essential of any syphilis control program.

2. They will decrease the transmission of syphilis in marriage.

3. They will decrease the incidence of congenital syphilis.

4. By insistence on blood tests by "approved laboratories" they will raise the standard of laboratory performance throughout the country.

5. They will have a general educational value, in keeping the problem of syphilis clearly in the public mind.

The arguments against them, equally briefly, are:

1. In the diagnosis of syphilis, emphasis is laid almost wholly on the laboratory.

2. The specificity of serologic tests for syphilis in the best of hands (the originators of the tests themselves) is technically short of perfect. The recent serologic surveys of the United States Public Health Service and the American Society of Clinical Pathologists point out that (a) in the most competent hands (those of the originators), modern serologic tests provide from 0.2 to 1 per cent technical false positive results in known nonsyphilitic persons; (b) in laboratories other than those of the originators, performance may be as good as this; but an important number of laboratories (including more than one state or municipal health department laboratory), report technical false positive results in normal persons in from 1 to 10 per cent of those tested.

3. The specificity of serologic tests for syphilis is not only technically but also biologically short of perfection. Several diseases, including two reasonably prevalent in this country (malaria and infectious mononucleosis), cause biologic false positive results in a significant proportion of cases; and far too little positive modern information is available as to biologic false positive tests in many other conditions (e. g., vaccinia, after serum treatment, during fever or jaundice, etc.).

Moreover, evidence is accumulating to suggest that the blood of a small but as yet unknown proportion of perfectly normal persons may from time to time or permanently contain enough reagin or reagin-like substance to cause a transitory or permanent biologic false positive serologic test.

Therefore, in view of the second and third items, a considerable number of nonsyphilitic persons will be caused undue alarm, delay in marriage, and expense in unraveling the significance of false positive or doubtful results. The case reports of Stokes and Ingraham make clear that this is already happening, as other consulting syphilologists also can testify.

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63. Nelson, N. A.: Marriage and the Laboratory, Am. J. Syph., Gonor. & Ven. Dis. **23**:288 (May) 1939.

64. Stokes, J. H., and Ingraham, N. R., Jr.: Syphilis and the Law, with Discussion of False Positive Blood Serologic Tests, J. A. M. A. **112**:1133 (March 25) 1939.

65. Premarital and Prenatal Examination Laws for Syphilis, editorial, Am. J. Syph., Gonor. & Ven. Dis. **23**:386 (May) 1939.

4. The blood test is a wholly invalid indicator of infectiousness or noninfectiousness in syphilis.

5. Four States (Wisconsin, Illinois, Michigan, and Kentucky) have rushed so headlong into such legislation as to forbid the marriage of a person with a positive serologic test for syphilis at any time, regardless of his actual or potential infectiousness. Their hasty, misguided, and unjust legislative example may be followed by other states.

6. Where the law requires blood test evidence to be reinforced by clinical examination, it is even more faulty, since, at an estimate, 95 per cent of all patients infected with syphilis will show no gross physical evidence of the disease at the time of life when marriage is usually contracted.

7. The law will not serve its purpose in preventing the spread of syphilis within marriage. Premarital intercourse is already so frequent as to make the law an effort to lock the stable door after the horse is stolen. In the social and economic groups having the highest incidence of syphilis, the incidence of common-law marriages and of illegitimacy will be increased.

Brunet and Salberg [66] have analyzed statistically the information as to age, sex life, pregnancies, abortions and venereal disease obtained from 913 women who applied to their clinic for compulsory premarital examinations. Only 177 (19 per cent) of the group were found to have intact hymens. In spite of the large number who had apparently been sexually exposed, only 2 per cent had positive Kahn or Wassermann tests.

In Wisconsin, Lorenz [67] found only 295 persons (0.6 per cent) with positive serologic tests for syphilis among 45,992 examined as a routine under the antenuptial blood test law.

*Compulsory vs. Voluntary Methods in the Control of Syphilis.*—There is ample evidence of a material decline in the incidence of fresh syphilitic infection in northern and northwestern European countries. For the Scandinavian countries, Holland and Great Britain, the data are documented afresh by a British commission (Harrison and associates [68]) and for Russia in a striking paper by Danyushevsky.[69] Harrison and the British committee were especially interested in the trends in the

66. Brunet, W. M., and Salbberg, J. B.: The Findings in Nine Hundred and Thirteen Premarital Examinations, Am. J. Syph., Gonor. & Ven. Dis. **23**:300 (May) 1939.

67. Lorenz, W. F.: Antenuptial Blood Tests in Wisconsin, Wisconsin M. J. **38**:318 (April) 1939.

68. Harrison, L. W.; Ward, D. C. L.; Ferguson, T., and Rorke, M.: Report on Anti-Venereal Measures in Certain Scandinavian Countries and Holland, Ministry of Health Reports on Public Health and Medical Subjects, no. 83, London, His Majesty's Stationery Office, 1938.

69. Danyushevsky, S. M.: Combating Venereal Diseases in the U. S. S. R., Am. J. Syph., Gonor. & Ven. Dis. **23**:498 (July) 1939.

several countries studied because of differences in public health technic. They conclude:

> Considering that in the countries employing compulsory treatment [the Scandinavian countries] and in those which rely on a voluntary system [Holland, England and Wales, Scotland] the degree of success in reducing the incidence of syphilis and of relative failure in gonorrhea are broadly similar, compulsory treatment does not seem to us to be a major factor influencing the results of the antivenereal measures in the countries where it is employed.

Harrison and his group believe that the fall in the incidence of syphilis is a direct reflection of the provision of adequate facilities for treatment and that such compulsory factors as legal insistence on treatment, on examination of contacts or of other members of the family (the epidemiologic approach to case-finding now so popular in the United States), on routine serologic testing or even on organized follow-up service, are relatively noncontributory.

In a lengthy but important article Towne[70] analyzes Harrison's British report. He points out that the statistical basis for a comparison between the figures for the incidence of syphilis in the several countries is inadequate and that certain of the statistical methods employed by the British committee may be invalid. He concludes that:

> Both compulsory and voluntary methods are needed. Each patient should, so far as possible, be dealt with on an individual basis through a friendly, educative, suasive approach. Clinics and also private practitioners should have the services of public health nurses, medical social workers, or other qualified field workers. Modern epidemiologic methods of finding sources of infection and new cases should be utilized. Public health authorities should maintain complete and intelligently analyzed statistical information concerning these diseases, both en masse and in respect to the relative effectiveness of different methods of control. To this end and for other purposes as well, the official reporting of all cases of syphilis and gonorrhea should be made mandatory. There should also be needed legal authority for the proper use, when and as necessary and particularly in cases of uncooperative patients, of compulsory measures concerning the carrying out of treatment and the prevention of new infections.

These and many other of the myriad papers of the past few years on public health measures for the control of syphilis raise an exceedingly interesting speculative problem. For public health authorities in the United States the model, on which their efforts are patterned, is found in Scandinavia and especially Sweden, where fresh syphilitic infections have fallen to a very low level. There has been a universal tendency to apply *post hoc ergo propter hoc* reasoning here, to wit: "Certain countries have adopted certain measures for the control of venereal disease; in these countries the incidence of syphilis has markedly decreased;

70. Towne, A. W.: Compulsory Versus Voluntary Methods of Venereal Disease Control in Scandinavia, Holland, and Great Britain, Am. J. Syph., Gonor. & Ven. Dis. **23**:348 (May) 1939.

therefore the decrease is directly due to the measures adopted." But, in a very large sense, this reasoning is faulty and uncontrolled. In practically all countries of the world except Sweden and Denmark there is a lack of accurate data as to the incidence of syphilis over a long period. Particularly is there a lack of worth while information as to the incidence or trend of syphilitic infection in various Southern and Southeastern European or in North or South American countries, where (at least until recently) there has been no organized effort at the control of syphilis. Where many control measures are simultaneously employed, it is impossible to evaluate the effect of any one.

The available figures for the world as a whole at least suggest that the incidence of syphilis may be declining, and possibly at the same relative rate in those countries which have not made a major public health effort as in those which have, and that the decline may be due not to the measures adopted for its control but to natural phenomena not as yet understood. This critical comment is not in the least intended to decry the present effort in this country to stamp out syphilis or to imply that it will not be successful; it is fair to assume that if the decline in syphilis in, e. g., Sweden has actually been due to the control measures adopted, those same methods or appropriate modifications of them will produce the same result in the United States. It is, however, suggested that in most countries, including this one, morbidity and mortality statistics do not yet permit sweeping conclusions as to the efficacy of control procedures.

### DRUGS

*Action of Arsphenamines and Bismuth Compounds in Vitro.*—There is now accumulating important information as to the action of antisyphilitic drugs. Since the time of the discovery of arsphenamine it has been thought that the action of this drug on S. pallida was indirect. Since arsphenamine was thought not to kill spirochetes in vitro, it was postulated that the drug was converted in vivo into an actively spirocheticidal substance. Eagle [71] has restudied the problem and has demonstrated that arsphenamine, neoarsphenamine, silver arsphenamine and arsenoxide are spirocheticidal in vitro. Varying dilutions of these drugs were added to an emulsion of rabbit chancre and were found in individual experiments to immobilize S. pallida in dilutions approximating 1:250,000 for neoarsphenamine, arsphenamine and silver arsphenamine and 1:1,000,000 for arsenoxide. The spirocheticidal property of the drugs in these dilutions was found to be affected by (1) the length of time the drug remained in contact with the emulsion (the longer the interval the higher the drug's effectiveness); (2) the tempera-

71. Eagle, H.: On the Spirocheticidal Action of Arsphenamines on Spirocheta Pallida in Vitro, J. Pharmacol. & Exper. Therap. **64**:164 (Oct.) 1938.

ture (the higher the temperature within the range of 23 to 37 C. [73.4 to 98.6 F.] the more organisms killed and the shorter the period required), and (3) the addition of tissue derivatives, which inhibited the in vitro spirocheticidal action. Serum has only a slight inhibitory effect.

The action of bismuth in syphilis has been as poorly understood as that of arsenic, and, like arsenic, bismuth has been thought not to be directly spirocheticidal. Levaditi [72] attributed its action to the formation in vivo of a hypothetic bismuth-protein complex, "bismoxyl." Kolle and Evers,[73] on the other hand, presented evidence that bismuth is not actively spirocheticidal even in vivo and that it merely inhibits the growth of S. pallida. Now, however, Eagle [74] shows that, like arsenic, bismuth is probably directly spirocheticidal. He says:

> It would appear from the experiments here described that bismuth compounds kill pathogenic *Sp. pallida in vitro*. The organisms are immobilized, become noninfectious for rabbits, and are presumably dead. . . . There was no indication that tissue derivatives contributed in any way to the antispirochetal action of bismuth; on the contrary, as in the case of the arsphenamines, tissue extractives regularly and markedly inhibited this activity. As much as an eighty-fold decrease in the apparent efficacy of a bismuth preparation could be produced by increasing the concentration of tissue extractives.
>
> Two of six soluble bismuth preparations commercially available formed precipitates on addition to serum or tissue extracts; their activity *in vitro* was correspondingly impaired. The remaining four preparations were approximately ¼ to 1/28 as active as "arsenoxide," the bismuth and arsenic being compared on a molar basis in each instance. The possibility must therefore be considered that bismuth compounds act neither as catalysts, inhibitors, nor precursor substances, but that the therapeutic action of bismuth in syphilis depends in part, and perhaps primarily, on its direct spirocheticidal action on *Sp. pallida*.

In a later paper Eagle [75] shows that the concentrations in which arsenoxide, arsphenamine, neoarsphenamine and bismuth destroy S. pallida in vitro are comparable to the concentrations obtainable in the human body with the usual therapeutic doses. Arsenoxide is spirocheticidal in dilutions of 1:650,000 to 1:4,700,000 when mixed in vitro with edema fluid from a rabbit chancre and allowed to remain

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72. Levaditi, C., and Howard, A.: Activation des propriétés curatives du bismuth dans la syphilis sous l'influence de tissus riches en glutathion, Compt. rend. Soc. de biol. **100**:469 (Feb. 22) 1929.

73. Kolle, W., and Evers, E.: Experimentelle Untersuchungen über Syphilis und Rekurrensspirochætose: III. Experimentelles über Syphilisinfektion ohne Symptome, Deutsche med. Wchnschr. **52**:557 (April 2) 1926.

74. Eagle, H.: On the Spirocheticidal Action of Bismuth Compounds on Pathogenic Spirocheta Pallida in Vitro, Bull. Johns Hopkins Hosp. **63**:305 (Nov.) 1938.

75. Eagle, H.: The Minimal Effective Concentration of Arsenic and Bismuth Compounds on T. Pallidum in Vitro in Relation to the Therapeutic Dose, Am. J. Syph., Gonor. & Ven. Dis. **23**:310 (May) 1939.

at room temperature from one and one-quarter to two and one-half hours. Arsphenamine, neoarsphenamine and silver arsphenamine are likewise effectively spirocheticidal in dilutions of 1:250,000 to 1:1,250,000. Water-soluble bismuth preparations are spirocheticidal in dilutions of 1:50,000 to 1:225,000. If 0.4 Gm. of arsphenamine, 0.05 Gm. of arsenoxide or an amount of a bismuth compound containing 0.04 Gm. of bismuth metal is injected into a patient weighing 70 Kg., these doses should represent concentrations in the body fluids, if the drugs are evenly distributed throughout, of 1:100,000, 1:800,000 and 1:1,000,000, respectively. This concentration obtainable for the arsenicals is sufficient to be directly spirocheticidal in vivo.

The agreement between the bismuth concentrations actually attained in the circulating blood and organs and the experimentally determined effective concentrations in vitro is surprisingly good, and constitutes strong evidence for the thesis that the therepeutic effect of bismuth in syphilis rests on a direct spirocheticidal action similar to that observed in the test tube.

Carrying further his studies of the action of the arsenicals and heavy metals, Eagle [76] presented papers before the American Society of Pharmacology and Experimental Therapeutics which have so far been published only in abstract, the detailed experiments to follow. Here he shows that:

The antispirochetal action *in vitro* of "arsenoxide" (m-amino-p-hydroxyphenylarsenoxide) and bismuth compounds was unaffected by the removal of molecular oxygen [from the spirochete-arsenical mixture] and is probably due to these compounds as such. In marked contrast, neoarsphenamine, which is highly spirocheticidal when dissolved aerobically, was negligibly so when dissolved and tested under nitrogen in the absence of oxygen. Its relatively marked antispirochetal action when tested aerobically (25 to 60 times that observed under nitrogen) is apparently due to its oxidation by molecular oxygen to other directly spirocheticidal compounds. This oxidation did not require the presence of tissue derivatives and proceeded so rapidly that solutions became actively spirocheticidal within 3 to 5 minutes.

Commercial arsphenamine and silver arsphenamine were intermediate between arsenoxide and neoarsphenamine, in that although ⅔ to ⅞ of their antispirochetal activity *in vitro* was due to oxidation products, there was a small but significant residual activity in the absence of oxygen. In the case of arsphenamine, a large part of this residual activity was accounted for by "arsenoxide" or by "arsenoxide"-like substances present as an impurity.

Sulfhydryl compounds (cysteine, glutathione, and thioglycollic acid) added in sufficient excess to arsphenamines, "arsenoxide," bismuth, or mercury compounds, almost completely abolished their antispirochetal action in vitro. The large excess which was necessary to cause complete inactivation of the arsenical suggests that the addition compound may be readily hydrolyzed. Thiamin chloride and methionine, which contain a —S— rather than a —SH group, had no inhibitory effect.

76. Eagle, H.: The Effects of Molecular Oxygen and Sulfhydryl Compounds on the Antispirochetal Action of Arsenic, Bismuth and Mercury Compounds in Vitro, J. Pharmacol. & Exper. Therap. **66**:10 (May) 1939.

These findings are of interest in relation to the thesis that the antispirochetal action of arsenic, bismuth, and mercury compounds may rest on their common affinity for sulfhydryl groups in the *T. pallidum*.

*Neoarsphenamine.*—Probey and Harrison [77] find that the instability of neoarsphenamine due to heat increases directly with the moisture content of the drug.

*Solusalvarsan.*—This drug (3, 4-diacetylamino-4-hydroxyarsenobenzene-2-sodium glycocholate), well known in Germany, has been little used in this country. It is said to have two advantages over other arsphenamines: it does not become oxidized when exposed to air, and it may be administered by the intramuscular route. Wendlberger and Hrad [78] report the results of treatment of 159 patients with this drug. To 90 patients it was given twice weekly by the intramuscular route in a dose of 0.4 to 0.5 Gm. Seventeen of the 90 patients so treated reacted with dermatitis, of whom 5 had erythema of the ninth day, 6 late erythema, either morbilliform or scarlatiniform, and 6 severe exfoliative dermatitis. Among 69 patients treated intravenously, 3 had erythema of the ninth day, 5 late erythema and 2 exfoliative dermatitis. Aside from causing these cutaneous reactions the drug was satisfactory in the treatment of primary, secondary, late and congenital syphilis. There was reversal of the serologic test in 33 per cent of the cases in which this drug was used in treatment.

*Mapharsen.*—Astrachan and Wise [79] used mapharsen in the treatment of 118 patients who had latent syphilis and studied the clinical and serologic effect. In many patients there was disappearance of various symptoms. The serologic response was favorable in 65 of the 101 patients investigated. Fifteen patients whose serologic reactions did not improve were later found to have neurosyphilis. Twenty-eight of the 118 patients experienced some type of reaction to the treatment. Of these, many had mild gastrointestinal disturbance; 7 suffered from intense pruritus, 2 from urticaria, 1 from purpura, 1 from herpes zoster, 7 from erythematous eruptions and 1 from a fixed dermatitis. In only 5 of the 28 instances of reaction was it necessary, however, to discontinue the use of the drug.

Phillips and Knoepp [80] found neither improvement nor activation of tuberculous lesions in 34 syphilitic patients treated with mapharsen.

77. Probey, T. F., and Harrison, W. T.: The Effect of Artificial Temperatures on Stability of Neoarsphenamine, Pub. Health Rep. **54**:228 (Feb. 10) 1939.

78. Wendlberger, J., and Hrad, O.: Zur Vertäglichkeit und Wirksamkeit des Solu-Salvarsans bei Luetikern, Dermat. Wchnschr. **108**:125 (Feb. 4) 1939.

79. Astrachan, G. D., and Wise, F.: Further Experiences with Mapharsen: Its Use in Latent Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **22**:470 (July) 1938.

80. Phillips, J. R., and Knoepp, L. F.: Control of Syphilis in Tuberculosis, South. M. J. **31**:1295 (Dec.) 1938.

*Acetarsone.*—Robinson and Robinson [81] analyze the results obtained in 32 adult syphilitic patients treated orally with acetarsone. Two patients had primary syphilis, with positive serum reactions, 23 patients had moist secondary lesions, and 7 had latent syphilis. The dose was 1 to 3 Gm. daily. One gram of acetarsone will not cause disappearance of S. pallida from surface lesions, but 2 Gm. causes the disappearance of the organisms in twenty-four hours. The serologic tests for syphilis became negative in only 4 of the 25 cases of early syphilis. The incidence of reactions from the drug was so high as to preclude its further use. Of the 32 patients, 4 reacted with dermatitis, 4 with diarrhea, 3 with an increase in the icterus index and 1 with a severe gastrointestinal disturbance. Of the entire group 37.5 per cent had serious reactions.

The use of acetarsone in congenital syphilis will be discussed later.

*Bismuth.*—(*a*) Oral Administration. There is still little satisfactory experimental or clinical evidence to support the view that orally administered preparations of bismuth are effective in the treatment of syphilis. In a series of papers Hanzlik and associates [82] have continued their study of sobisminol. This drug may be given either orally or by intramuscular injection. Administered by either route, it is rapidly absorbed and relatively slowly excreted, producing the desirable combination for efficient antisyphilitic treatment of rapid penetration and sustained circulation of bismuth. Quantities by mouth far in excess of the average therapeutic dose are tolerated by experimental animals, necropsy showing tissue changes to be negligible or absent. The animals, however, show anorexia and loss of weight. The drug causes no appreciable changes in the bones of young white rats.

Shaw, Kemp and Fitzgerald [83] treated 15 syphilitic rabbits orally with sobisminol, 12 of which survived the experiment. Treatment was

81. Robinson, H. M., and Robinson, H. M., Jr.: Acid Acetarsone Orally in Treatment of Acquired Syphilis in Adults, Am. J. Syph., Gonor. & Ven. Dis. **23:** 188 (March) 1939.

82. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sobisminol: Toxicity, Tolerance and Irritation According to Different Channels of Administration, J. Pharmacol. & Exper. Therap. **62:**372 (April) 1938. Hanzlik, P. J., and Lehman, A. J.: Continued Voluntary Drinking of Sobisminol: General Effects, ibid. **62:**389 (April) 1938. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Excretion of Bismuth After Intramuscular Injection of Sobisminol, ibid. **62:**404 (April) 1938; Intramuscular Injection of Sobisminol: Absorption and Distribution of Bismuth, ibid. **62:**413 (April) 1938. Lehman, A. J., and Dock, W.: Effects of Drinking Sobisminol on Skeletal Changes in Growing White Rats, ibid. **63:**88 (May) 1938.

83. Shaw, C.; Kemp, J. E., and Fitzgerald, E. M.: Sobisminol (Sodium Bismuthate Soluble) in the Treatment of Experimental Rabbit Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **23:**210 (March) 1939.

given three times a week for five weeks, the weekly dose being that prescribed by Hanzlik, 219.9 mg. per kilogram measured in metallic bismuth. From one hundred and nineteen to two hundred and thirty-seven days after the conclusion of treatment the popliteal lymph nodes of 6 of the 12 surviving rabbits, on transfer, transmitted the infection to other rabbits. The authors conclude that sobisminol in the doses used is not satisfactory for the treatment of late syphilis in rabbits.

Because of the conflicting reports regarding the value of orally administered bismuth compounds, Stratton [84] attempted experimentally to determine the amount of bismuth absorbed by measuring the urinary excretion of the element in rabbits. Four bismuth preparations were used, bismutrate (bismuth chloride treated with liver extract), sobisminol, potassium bismuth tartrate and bisiodide. The amount of bismuth excreted in the urine of rabbits following the administration of a single dose of a bismuth compound by mouth, whether containing 20 mg. or 200 mg. of bismuth metal per kilogram of body weight, was satisfactory for bismutrate and sobisminol, less so for potassium bismuth tartrate and not at all for bisiodide. When fourteen daily doses of a compound containing 20 mg. of bismuth metal per kilogram were given, however, there was no proportionate increase in the amount of bismuth excreted, and the daily average amount excreted was far below the level estimated to be necessary for definite antisyphilitic value.

(*b*) Concentration in Tissues. Sollmann, Cole and Henderson [85] have quantitatively determined at autopsy the content and concentration of bismuth in the viscera of patients who had been clinically treated with preparations of this metal. The concentration of bismuth in viscera is dependent on the total amount of bismuth administered. If one viscus was high in bismuth, all other viscera were proportionately high. Sollmann and Henderson [86] then quantitatively determined the concentration and the total content of bismuth in the viscera of dogs treated with a single dose of one or another of twelve different bismuth compounds.

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84. Stratton, E. K.: The Absorption and Elimination of Bismuth Following Its Oral Administration to Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **22**:728 (Nov.) 1938.

85. Sollmann, T.; Cole, H. N., and Henderson, K.: Clinical Excretion of Bismuth; VII. The Autopsy Distribution of Bismuth in Patients After Clinical Bismuth Treatments, Am. J. Syph., Gonor. & Ven. Dis. **22**:555 (Sept.) 1938.

86. Sollmann, T., and Henderson, K.: Bismuth Studies: VII. Bismuth Distribution in Dogs Following Intramuscular Injection of a Single Dose of Various Bismuth Preparations, Am. J. Syph., Gonor. & Ven. Dis. **22**:738 (Nov.) 1938.

Cole, Sollmann and Henderson [87] give a summary of their experiments as an aid in the choice of a bismuth preparation. They list the commonly used bismuth compounds and recommend the intervals of time at which they should be given in order to maintain a spirocheticidal level of the drug in the blood. Any preparation which furnishes a daily urinary excretion of from 2 to 4 mg. of bismuth is thought to be a valuable antisyphilitic agent. They say:

> In choosing the bismuth preparation. . . . the physician should consider what is indicated in the particular patient.
>
> *For rapid bismuth effect:*
>
> Sodium bismuth tartrate in water: Injections intramuscularly three times a week
>
> Sobisminol, Iodobismitol } Injections twice weekly
>
> If the patient can be persuaded to return twice a week for injections, probably the most efficient preparations in terms of high bismuth excretion are sobisminol and iodobismitol.
>
> *For a somewhat slower but efficient bismuth effect:*
>
> Biliposol, Bismocymol } Injections every five days to once a week
>
> *For an effect slow in building up, but eventually sustained:*
>
> Injections of oil suspensions of:
>
> Sodium potassium bismuth tartrate, Bismuth subsalicylate } Once weekly

(*c*) Toxicity, Absorption and Excretion of Bismuth. Kolmer, Brown and Rule [88] have made a comparative study in lower animals of the toxicity, absorption, excretion and therapeutic effectiveness of thirteen regularly used bismuth compounds. Water-soluble bismuth compounds were more toxic than oil-soluble, and both were more toxic than water-soluble and water-insoluble compounds suspended in oil. In general the water-soluble and the oil-soluble compounds produce nephritis more frequently than the insoluble compounds. The excretion in urine was generally dependent on the rate of absorption and the concentration of the drug in the blood. The water-soluble compounds were excreted more rapidly. The spirocheticidal activity of the compounds was dependent on the amount of elemental bismuth present in

87. Cole, H. N.; Sollmann, T., and Henderson, K.: The Choice of a Bismuth Preparation: Clinical Résumé of Excretion and Retention Studies, Am. J. Syph., Gonor. & Ven. Dis. **23**:143 (March) 1939.

88. Kolmer, J. A.; Brown, H., and Rule, A. M.: Studies in the Bismuth Therapy of Syphilis: I. A Comparative Study of the Toxicity and Therapeutic Activity of Bismuth Compounds Commonly Employed in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **23**:7 (Jan.) 1939.

the compound, the chemical structure and the rates of absorption and excretion, and these in turn were dependent on the solubility in the menstruum employed and the solubility in the tissues. The bismuth compounds suspended in oil had by far the highest therapeutic indexes, ranging from 100 to 166. The authors feel that there is an optimum concentration of bismuth in the blood and that this is best obtained by the use of a bismuth compound which is not so rapidly absorbed and excreted as are the water-soluble compounds but which has a relatively high percentage of elemental bismuth and is absorbed and excreted slowly, as are the oil-suspended preparations.

(*d*) Treatment with Bismuth Compounds in Combination. Sollmann, Cole and Henderson [89] calculated the amount of bismuth excreted in the urine of patients when they were given (1) bismuth subsalicylate in oil alone, (2) bismuth subsalicylate in oil plus iodobismitol and (3) bismuth subsalicylate plus sobisminol. The daily urinary excretion of bismuth after weekly injections of bismuth in oil did not reach 1 mg. before the third week and 2 mg. before the sixth week. However:

> A graded sequence of injections of soluble bismuth preparations (iodobismitol and sobisminol) with continued weekly injections of bismuth salicylate produces a high initial concentration of bismuth as reflected in the urinary excretion, which reaches at the end of two weeks a level of from 4 to 12 mg. of bismuth a day, according to the drugs used. This concentration then falls so as to join the slowly ascending curve characteristic of salicylate injections about the end of from five to seven weeks, so that the median level does not fall below 2 mg. of bismuth. . . . The sequence therefore secures the benefit of the intensive action of the water-soluble bismuth preparations in the early part of the course and the advantages of the convenience of salicylate injections in the latter part of the course.

The plan is recommended for use in the treatment of early syphilis, and when arsenic is badly tolerated.

*Other Drugs.*—Pavanati [90] was unable to demonstrate any spirocheticidal action of four rhodium salts (rhodium chloride, sodium rhodium chloride, potassium rhodium chloride, lithium rhodium chloride) in vitro. However, he treated syphilitic rabbits with these drugs, which were well tolerated whether injected by the intravenous or by the intramuscular route. After one dose of 50 mg. per kilogram the spirochetes disappeared from rabbit syphilomas in twelve to twenty-four hours, the lesions healed rapidly, and there were no relapses. Seven patients with early syphilis were then treated with rhodium chloride, 0.5 Gm. per dose. Spirochetes disappeared from the chancres

89. Sollmann, T.; Cole, H. N., and Henderson, K.: Combination Courses of Bismuth Administration, J. A. M. A. **111**:2175 (Dec. 10) 1938.

90. Pavanati, E.: Sali di rodio e sifilide (ricerche in vitro, sull' animale e sull' uomo), Gior. ital. di dermat. e sif. **79**:837 (Aug.) 1938.

in two to three days; there were no toxic symptoms. There is no record of a follow-up.

Kumasawa [91] found an alkaline solution of lead carbonate to be spirocheticidal but very toxic in rabbits. He then treated 6 syphilitic rabbits with lead acetate, 1 mg. per kilogram, injected intravenously, thrice weekly. Three animals died; the other three were "cured" after fifteen to twenty-one injections over a period of five to seven weeks. The drug was used subcutaneously in the same dosage with no deaths and with the same clinical results. Control animals treated at the same time with bismuth compounds were "cured" in a shorter period of time.

### UNTOWARD EFFECTS OF TREATMENT

*Erythema of the Ninth Day.*—Cañizares and Thomas [92] review the literature and report 11 cases of erythema of the ninth day. They feel that this reaction is a clinical entity, clearly distinct from the later appearing edematous exfoliative dermatitis. It may be a response of the autonomic nervous system to arsenic. It does not seem to be influenced by the dose administered, the type of trivalent arsenical, the mode of injection or the spacing of treatments. Blood counts and hepatic function tests gave no definite information. Passive transfer did not demonstrate the presence of antibodies. With proper precautionary measures, subsequent arsenical treatment is usually well tolerated.

*Agranulocytosis After Treatment with Neoarsphenamine.*—Goldberg [93] reports a single case confirming the suggestion of Falconer, Epstein and Wever (mentioned in the 1937 review [1c]) that patients in whom blood dyscrasias develop after treatment with an arsphenamine may nevertheless tolerate mapharsen.

Montanaro [94] and Lancellotti,[95] working together, have studied in rabbits and guinea pigs (the former from the pathologic, the latter from the hematologic, standpoint) the injury to the blood and blood-forming organs produced by the arsphenamines. While slight evidences

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91. Kumasawa, M.: Experimentelle Untersuchungen über die antiluetische Wirkung von Bleisalzen, Fukuoka acta med. (Abstr. Sect.) **31**:177 (Dec.) 1938.

92. Cañizares, O., and Thomas, E. W.: Early Acute Arsenical Erythemas: A Study of Eleven Cases of the "Erythema of the Ninth Day" of Milian, Arch. Dermat. & Syph. **39**:867 (May) 1939.

93. Goldberg, M.: Mapharsen as a Substitute for Neoarsphenamine in Agranulocytic Angina Following Neoarsphenamine Therapy in a Pregnant Syphilitic Woman, Am. J. Syph., Gonor. & Ven. Dis. **23**:79 (Jan.) 1939.

94. Montanaro, E.: Contributo sperimentale alla conoscenza delle lesioni da arsenobenzolo degli organi ematopoietici, Policlinico (sez. med.) **45**:553 (Nov.) 1938.

95. Lancellotti, M.: Contributo sperimentale alla conoscenza delle lesioni Sanguigne da arsenobenzolo, Policlinico (sez. med.) **45**:573 (Nov.) 1938.

of damage were found, the authors were unable to produce a genuine blood dyscrasia.

*Gastrointestinal Reactions.*—Irgang [96] discusses at some length gastrointestinal reactions following the intravenous injection of trivalent arsenicals. He believes that these reactions, the nitritoid crises, arsphenamine shock, dermatitis, thrombopenia, purpura and hepatitis are related to an allergic state.

*Hemorrhagic Encephalitis.*—Paley and Pleshette [97] report another case of hemorrhagic encephalitis following injections of neoarsphenamine in a pregnant woman. In the literature they find reports of 158 cases of hemorrhagic encephalitis. The patients more commonly were males; but of the females who presented this condition, 70 per cent were pregnant. In most instances the complication occurred after the first two or three injections of the arsenical and after a dose of 0.45 Gm. or more.

*Relation of Vitamin C to Arsenical Reactions.*—There is increasing interest in the role played by vitamin C in arsenical dermatitis. Practically all of the literature of the past two years deals with clinical impressions. The few papers describing animal experimentation are confusing, one author believing the lack of vitamin C to be responsible for toxic reactions in animals, and another that excess of vitamin C renders the animal more likely to have reactions. For example, Cohen [98] feels that before experimental work on the relation of vitamin C to toxic reactions in animals can be regarded as valid, certain basic conditions must be adhered to, namely:

1. The diet must be adequate in all respects except for vitamin C.
2. The animal must have sufficient food to avoid starvation.
3. The ration of vitamin C must be planned upon a sliding scale according to the tooth-protective ration.

After fulfilling these conditions, Cohen could find no relationship between the vitamin C content of the diet and sensitivity of the skin to neoarsphenamine.

Karolyi,[99] however, feels differently about the role played by vitamin C in relation to the toxicity of arsphenamine. He gave to one

96. Irgang, S.: Gastric Intolerance Accompanying Arsphenamine Therapy: A Discussion of Its Etiology, Prevention, and Treatment with Case Reports, Am. J. Syph., Gonor. & Ven. Dis. **23**:241 (March) 1939.

97. Paley, S. S., and Pleshette, N.: Hemorrhagic Encephalitis in Pregnancy Following Antisyphilitic Therapy with Neoarsphenamine, Am. J. Syph., Gonor. & Ven. Dis. **23**:69 (Jan.) 1939.

98. Cohen, M. B.: Vitamin C Deficiency: Sensitivity to Neoarsphenamine and Anaphylactic Shock, J. Allergy **10**:15 (Nov.) 1938.

99. Karolyi, I.: The Effects of Ascorbic Acid and Glycocoll on Chronic Arsenobenzol Poisoning, Orvosi hetil. **82**:829 (Aug.) 1938.

series of white rats 25 mg. of ascorbic acid and 75 mg. of aminoacetic acid daily for ten days, after which he gave arsphenamine in increasing doses, 7 to 40 mg., twice weekly, at the same time continuing to administer ascorbic acid and aminoacetic acid on the day of treatment. A control series was given arsphenamine alone in the same dosage. The animals receiving ascorbic acid lived longer than those receiving arsphenamine alone.

*Solvents for the Arsphenamines.*—In an effort to decrease the incidence of toxic reactions from the arsphenamines, there have been many proposals that a solution of some supposedly detoxifying substance, e. g., dextrose, sodium thiosulphate, aminoacetic acid, various proprietary substances derived from liver (the latter especially in Germany) or one or another vitamin, be used as a solvent for the arsenical drug. A prototype of these studies is described in a paper by Shaw,[100] who used sodium dehydrocholate as a solvent for neoarsphenamine in the effort to prevent gastrointestinal and hepatic reactions. Twelve patients who habitually suffered from nausea and vomiting after receiving neoarsphenamine tolerated the drug well when it was dissolved in a 5 per cent solution of sodium dehydrocholate.

It is unfortunate that, with few if any exceptions, such clinical efforts are unsupported by experimental studies to show that the toxicity of arsphenamine is decreased by the use of the special solvent and, equally important, that if toxicity is decreased, it is not accompanied by a parallel decrease in therapeutic efficiency. Obviously, there is no advantage in the elimination of reactions, especially minor ones, if at the same time the spirocheticidal drug is rendered wholly or partially inert.

*Desensitization with Arsphenamine.*—The consensus is that patients in whom cutaneous sensitivity to the arsphenamines develops cannot be desensitized. Desensitization has often been attempted by the repeated injection of small intravenous or subcutaneous doses. Jacobson and Brill[101] describe a new method of desensitization: the intracutaneous injection every other day of 0.15 cc. of varying dilutions of arsphenamine. For the first three injections the dilution is 1:1,000,000; for the next two, 1:10,000; for the next two, 1:1,000, and for the eighth and last, 1:100. If there is a marked local or general reaction in the course of these injections, the dose is lowered, or the interval between doses is increased, or both. An average of seventeen to twenty-two

100. Shaw, C.: Sodium Dehydrocholate Solution as a Solvent for Neoarsphenamine in the Treatment of Syphilis, J. Lab. & Clin. Med. **24**:624 (March) 1939.

101. Jacobson, A., and Brill, M.: The Intracutaneous Method of Desensitizing with the Arsphenamines, Vestnik venerol. i dermat. **6**:49, 1938.

days is required to desensitize a patient. If there is no reaction in the course of the eight intracutaneous injections, therapeutic doses of the drug may be given. Desensitization was attempted with patients. Two patients had exfoliative dermatitis, 3 scarlatiniform eruptions, 3 morbilliform eruptions, 5 urticaria and 1 a fixed dermatitis. Of the 14 patients, 11 were satisfactorily desensitized and could be given therapeutic doses of arsphenamine; 3 could not be desensitized at the first attempt, but 1 of these was desensitized after the described technic had been repeated several times. One of the 2 patients who could not be desensitized was a patient with urticaria, and the other had a fixed dermatitis. The two patients who had exfoliative dermatitis were satisfactorily desensitized.

Unfortunately, it is not certain that all the patients studied were originally sensitized. The American concept of sensitization dermatitis usually does not include scarlatiniform, morbilliform and urticarial eruptions.

*Toxicity of Tryparsamide.*—An editorial commentator [102] says:

> Tryparsamide (the sodium salt of N-phenyl-glycineamide p-arsonic acid) has been used in the treatment of neurosyphilis and trypanosomiasis since 1923. For a dozen or more years following its introduction, all workers were impressed by the fact that it produced few or no reactions except those involving the optic nerves. . . .
>
> Constitutional reactions from the drug were for many years so rare that Moore, writing in 1933, said: "The use of tryparsamide is singularly free from constitutional reactions of any sort. . . . Only two instances of post-tryparsamide jaundice have occurred in our clinic. . . . Dermatitis does not occur after this drug." Stokes, in 1935, mentioned 4 cases of post-tryparsamide jaundice and 3 of dermatitis (all but one from the literature); but he said: "I have personally never observed a single significant complication of tryparsamide therapy as such, other than those involving the optic tract.
>
> Within the past few years, however, a distinct change in the reactivity of tryparsamide apparently has occurred. Mild to moderately severe immediate or slightly delayed reactions, such as malaise, chilliness or actual chills, nausea and vomiting, and prostration, formerly completely absent, now seem to occur in a considerable number of cases. The literature since 1933 contains at least 12 direct references to post-tryparsamide jaundice, dermatitis, or other constitutional reactions. . . . Traenkle and Dolce [103] report two cases of fatal liver necrosis following tryparsamide; and . . . Golz [104] reports a case of severe exfoliative

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102. The Toxicity of Tryparsamide, editorial, Am. J. Syph., Gonor. & Ven. Dis. **23**:389 (May) 1939.

103. Traenkle, H. L., and Dolce, F. A.: Acute Fatal Liver Necrosis Following Tryparsamide Administration: A Report of Two Cases, Am. J. Syph., Gonor. & Ven. Dis. **23**:228 (March) 1939.

104. Golz, H. H.: Sensitivity to Arsenical Drugs: Report of an Unusual Case Exhibiting Sensitivity to Both Trivalent and Pentavalent Arsenic, Am. J. Syph., Gonor. & Ven. Dis. **23**:344 (May) 1939.

dermatitis in a patient previously sensitized to the arsphenamines. In the Johns Hopkins Hospital clinic, to 1936, had occurred 6 cases of post-tryparsamide jaundice (Soffer), an incidence of 0.22 per cent of patients treated, as contrasted to a similar incidence of 0.98 per cent for arsphenamine and 0.63 per cent for neoarsphenamine.

It is noteworthy that practically all of these constitutional reactions, mild and serious, have appeared within the last five years of use of tryparsamide, which for the previous ten years had been nearly or completely free from them. This is a curious and so far unexplained phenomenon of chemotherapy. It has been observed with other antisyphilitic drugs than tryparsamide, and indeed with other compounds than antisyphilitic drugs. Presumably it is due to some slight variation in the raw materials used in drug synthesis or in minor variations which creep into the method of manufacture. These in turn may result either in the presence of traces of impurities or in an end product which, while apparently chemically identical with the original nontoxic product, behaves pharmacologically in a slightly different manner in the human body. In the case of tryparsamide, the increased incidence of constitutional reactions has been a matter of serious concern. . . .

Astrachan and Franks [105] report a typical nitritoid reaction following injections of tryparsamide.

*Jaundice from Bismuth.*—Nomland, Skolnick and McLellan [106] have studied jaundice occurring during antisyphilitic therapy in 75 patients, in 32 of whom they believe the reaction to have been due to bismuth. Of these 32 patients, 10 had received no arsenical; 22 had been given arsphenamine but not for twelve weeks or longer prior to the development of jaundice. Other conditions which might have caused jaundice in these patients were considered and ruled out as probably not responsible. The authors calculated that the probable incidence of bismuth-induced jaundice in their clinic over a period of five years was 1 in 2,242 injections of bismuth compounds, whereas the incidence of arsphenamine-induced jaundice was 1 in 951 injections. Most of these patients were subsequently given further bismuth treatment without recurrence of jaundice.

Lane [107] analyzed the data on 100 patients in whom jaundice occurred during antisyphilitic treatment. Two patients of this group had received no antisyphilitic drugs other than preparations of bismuth. In 8 patients jaundice developed during bismuth therapy more than

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105. Astrachan, G. D., and Franks, A. G.: Nitritoid Reaction Following an Injection of Tryparsamide, Arch. Dermat. & Syph. **38**:949 (Dec.) 1938.

106. Nomland, R.; Skolnick, E. A., and McLellan, L. L.: Jaundice from Bismuth Compounds Used in the Therapy of Syphilis: Report of Thirty-Two Cases, J. A. M. A. **111**:19 (July 2) 1938.

107. Lane, C. G.: Jaundice Occurring During the Treatment of Syphilis, Arch. Dermat. & Syph. **39**:278 (Feb.) 1939.

twelve weeks after the last dose of an arsenical. Lane likewise feels that bismuth may be a cause of jaundice.

### PATHOLOGIC OBSERVATIONS

Bell [108] estimates the frequency with which pathologic evidence of syphilis was encountered among 27,872 postmortem examinations in Minneapolis hospitals. He points out that obvious anatomic evidence of syphilis is less frequent than the positive serologic test, but unfortunately he has made no attempt to correlate clinical findings with observations made at necropsy. His data do not, therefore, answer the important questions: What is the probable mortality from syphilis if the patients are untreated? If they are treated, what are the effects of varying amounts and kinds of treatment? Syphilis was observed in 2.77 per cent of the 27,872 necropsies and was shown to be the direct cause of death in 2.5 per cent. Among infants congenital syphilis, and among adults cardiovascular syphilis and neurosyphilis, accounted for the large majority of deaths from syphilis. Especially interesting is the fact that in the fourth decade of life, in which the general death rate is low, syphilis accounted for 8 per cent of the deaths among men.

### EARLY SYPHILIS

*Diagnosis.*—Clinicians have long been aware that simultaneous infection with gonorrhea and syphilis might occur, the latter being either symptomless or represented by an intraurethral chancre masked by the gonorrheal discharge. Friedman [109] describes a simple method by which a purulent urethral discharge may be satisfactorily examined for S. pallida. The discharge is drawn up into a fine capillary tube about 12 cm. long. One end is sealed by flame, and the tube is then centrifuged at low speed, 1,000 revolutions per minute, for ten minutes, which removes cellular debris and leaves S. pallida, if present, in the supernatant fluid. The tube is broken just above the level of the cells and the clear fluid examined by dark field. This method was applied in 40 cases of acute gonorrheal urethritis. In 37 the results were negative, and subsequent physical examination and serologic tests did not indicate syphilitic infection. In another case, no spirochetes were found in the urethral discharge, no primary syphilitic lesion could be found in the patient, and the first serologic tests for syphilis were negative, but fifty-two days later such tests were positive. In the remaining 2 cases, S.

108. Bell, E. T.: Frequency with Which Syphilitic Lesions Are Encountered in Postmortem Examinations, Arch. Path. **26**:838 (Oct.) 1938.

109. Friedman, L.: A Method for the Darkfield Examination of Pus for Spirocheta Pallida, J. A. M. A. **112**:134 (Jan. 14) 1939.

pallida was found in the urethral discharge with the technic described. The method was also applied in a case of a penile lesion which bled freely. S. pallida was easily demonstrated after, though with considerable difficulty before, centrifugation.

In an article which deserves wide reading by clinicians and public health officers alike, Chambers and Scholtz [110] reiterate the advantages of diagnosing syphilis in the primary stage and point out why the results from the use of the dark field microscope are an incomplete solution of the problem of early diagnosis. The reasons are: (1) The physician needs special equipment and training; (2) it is difficult to obtain a proper specimen; (3) the patient objects to going to a public diagnostic laboratory, and (4) there are small chances of success with old and locally treated lesions. They believe that many of these difficulties may be obviated by routine biopsy of tissue removed from the edge of the suspected lesion, sectioned and stained by the method described by Krajian.[8] The practical advantages of this method are: The staining procedure requires only five to ten minutes; no expensive equipment is required; trauma is minimized; the patient is not required to go to a laboratory (to which the biopsy specimen in 10 per cent formaldehyde is forwarded), and the method is more accurate and practical for the rural physician than is the use of a capillary tube and indirect dark field examination.

Chambers and Scholtz studied 104 genital lesions suspected of being chancres; 86 were proved to be syphilitic. Of these, the stain gave negative results in only 1; dark field examination in this case gave positive results. In the other 85 cases in which S. pallida was found in stained section, dark field examination was not done in 6, but in the remainder was positive in only 46 (58 per cent). The superiority of the staining method suggests its wider applicability, and it would be distinctly worth while for the laboratory of some state health department to determine its value relative to the already available capillary tube–dark field technic.

*Involvement of Pelvic Nodes in Cervical Chancre.*—Hissard and Desmezerets [111] describe chancre of the cervix with satellite pelvic adenopathy as observed in 2 patients. De Gregorio and de Blasio,[112]

110. Chambers, S. O., and Scholtz, J. R.: Clinical Application of Stain for Spirochetes (Krajian), Arch. Dermat. & Syph. **38**:217 (Aug.) 1938.

111. Hissard and Desmezerets, C. V.: Chancres du col de l'utérus et adénopathie pelvienne, Bull. Soc. franç. de dermat. et syph. **45**:1731 (Nov.) 1938.

112. de Gregorio, E., and de Blasio, R.: Sull adenopatia pelvica satellite nella sifilosclerosi iniziale del collo dell utero, Rinasc. med. **15**:619 (Sept. 30) 1938.

Simon [113] and Delmas [114] each report a similar condition and describe the method of palpation. The involved lymph node is located in the broad ligament. If the fingers are placed high in the lateral fornix of the vagina with the plantar surfaces facing laterally and are slowly and gently brought anteriorly, the node may be felt.

*Osteitis in Patients with Early Syphilis.*—Osteitis and periostitis are rarely reported observed in patients with early syphilis. This is probably not because of the rarity of these conditions but mainly because patients with early syphilis who complain of headaches and pain in bones are not examined roentgenologically. Newman and Saunders [115] describe osteolytic changes in the skull and both tibias of a patient with secondary syphilis. Squires and Weiner [116] report, in a patient with secondary syphilis, several palpable small swellings of the skull, which on roentgen examination revealed circumscribed areas of decreased density. The reviewers can testify that destructive osteitis of the skull is not uncommonly found in patients with secondary syphilis if searched for.

*Massive Doses of Arsenicals in the Therapy of Early Syphilis.*—It has long been pointed out that the standard methods of treatment of syphilis are unsatisfactory in that they are too uncertain in results, too painful and disagreeable, too dangerous, too time consuming and too expensive. These defects have led to an intensive search by many experimental chemotherapists for new and improved methods of preparing arsenic and the heavy metals, or for entirely new products unrelated to those now in use; but so far, though many new drugs have been produced which in one respect or another possess moderate advantages over earlier products, the search for a chemical which would fulfil Ehrlich's original idea of an immediate sterilizing cure of the disease has not been successful. On the whole, while chemotherapeutic research has lessened some of the disagreeable features of treatment and has minimized both its danger and its expense, it has neither improved greatly on the results obtainable with Ehrlich's original arsphenamine ("salvarsan") combined with mercury nor materially shortened the time essential for successful treatment. Nevertheless, this type of research is continuing and properly should continue.

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113. Simon, C.: Trois cases de chancres syphilitiques du col de l'uterus accompagnés d'adénopathie pelvienne satellite nettement perceptible au toucher vaginal, Bull. Soc. franç. de dermat. et syph. **45**:604 (April) 1938.

114. Delmas, M.: Chancre syphilitique du col utérin avec ganglion satellite pelvien accessible par voie vaginale, Bull. Soc. franç. de dermat. et syph. **46**:713, 1939.

115. Newman, B. A., and Saunders, H. C.: Skeletal System Manifestations During Secondary Syphilis, New York State J. Med. **38**:788 (May 15) 1938.

116. Squires, J. B., and Weiner, H. L.: Osteitis in Early Syphilis: Report of a Case, Arch. Dermat. & Syph. **39**:830 (May) 1939.

Chargin, Leifer and Hyman [117] suggested in 1935 that early syphilis may be "cured" by a method of treatment which, though utilizing already available arsenical drugs (neoarsphenamine or mapharsen [118]), requires only five days for completion instead of the twelve to eighteen months necessary with the standard systems of treatment. The method involves the administration of large doses of the drug (with neoarsphenamine from five to six times, and with mapharsen from ten to fifteen times, the usual maximum therapeutic dose) given slowly by the continuous intravenous drip method over a five day period. It depends theoretically on the probable interrelationship between the concentration of the drug in the blood and tissue fluids and the spirocheticidal effect. When an arsenical drug is administered intravenously by the conventional divided dose technic its concentration in the blood rises momentarily to a very high level but promptly falls to much lower levels as the drug is removed from the circulation by the liver. With this standard method, a high concentration of the drug in the blood is probably not maintained for longer than an hour or two; thereafter the amount of therapeutically active drug in the body fluids is almost infinitesimal. To Chargin and his collaborators it seemed likely that a prolonged moderate concentration of the drug in the body might be more effective than a high concentration followed by a very much lower level, repeated at brief intervals.

This has been shown to be true of the administration of sulfanilamide and its derivatives for bacterial infections. There is a known critical concentration of sulfanilamide which must be maintained in the blood and tissues over a given period. If this concentration is too low, the bactericidal effect will not occur; if it is too briefly maintained, all the organisms will not have been destroyed, and relapse will follow.

In 1939 Hyman, Chargin and Leifer [119] report further that, of the 25 patients originally treated by this method, 15 were available for a five year follow-up. The cerebrospinal fluid of 13 patients was examined and found normal. The serologic tests of 11 patients remained negative after forty-two months. One patient certainly and another probably had been reinfected.

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117. Chargin, L.; Leifer, W., and Hyman, H. T.: Studies of Velocity and the Response of Intravenous Injections: V. The Application of the Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in the Treatment of Early Syphilis, J. A. M. A. **104**:878 (March 16) 1935.

118. The information as to mapharsen was obtained by personal communication with the authors.

119. Hyman, H. T.; Chargin, L., and Leifer, W.: Massive Dose Arsenotherapy of Syphilis by the Intravenous Drip Method: Five Year Observation, Am. J. M. Sc. **197**:480 (April) 1939.

Tzanck and collaborators[120] have published a number of papers on the massive dose method of treatment for syphilis (1.5 Gm. of neoarsphenamine per day for three consecutive days, each dose being administered slowly, drop by drop, over a three to five hour period). Their work was not as well controlled as that of the group aforementioned. However, as nearly as can be determined from these very repetitive papers, about 170 patients (with early and with late syphilis) have been treated by this technic with satisfactory immediate results as to disappearance of surface spirochetes, healing of lesions and prompt serologic reversal. The follow-up, as stated, was wholly inadequate. There have been at least 2 deaths directly attributable to the treatment.

The results of Hyman and collaborators, and even those of Tzanck and his associates, suggest that what is true of sulfanilamide and bacterial infection may also be true of arsenic and syphilis. It is important to point out, however, that much further study is essential before the new method may be applied generally.

There are as yet inadequate data as to the toxicity of large doses of arsenical drugs given by this method. In human beings given neoarsphenamine in the arbitrarily selected dose of 4 to 5 Gm. there was a high incidence of reactions, especially polyneuritis (35 per cent). It is desirable to redefine exactly in experimental animals the minimum lethal and the maximum tolerated dose with the new technic.

It is further desirable to redefine with the new method the minimum curative dose in experimental rabbit syphilis. With the usual single injection technic, the curative dose of arsphenamine is 10 to 12 mg. per kilogram and that of neoarsphenamine is 15 to 25 mg. per kilogram. The minimum curative dose of mapharsen is not definitely known, but it is certainly less than 6 mg. per kilogram, perhaps as little as 2 to 3 mg. per kilogram.

The clinical studies already carried out suggest that with the continuous intravenous drip method the minimum curative doses will be

120. Tzanck, A.: Traitement arsénical massif de la syphilis (par instillation goutte à goutte): Son interet prophylactique, Bull. Acad. de méd., Paris **119**: 257 (March) 1938. Tzanck, A.; Duperrat, R., and Lewi, S.: Le traitement novarsénical massif par instillation intraveineuse goutte à goutte, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:268 (Feb. 21) 1938; Arsénothérapie massive intraveineuse par instillation goutte à goutte (technique), J. de méd. de Paris **58**:341 (April 28) 1938. Tzanck, A.; Pautrat, J., and Moline, R.: Arsénothérapie massive par instillation veineuse goutte à goutte, ibid. **58**:283 (April 7) 1938. Tzanck, A.: Syndrome sécondaire mortel après traitement arsénical massif, Bull. Soc. franç. de dermat. et syph. **45**:487 (April) 1938; Le traitement massif arsénical de la syphilis, Bruxelles-méd. **18**:1642 (Oct. 30) 1938. Loeper, M.; Tzanck, A., and Brouet-Sainton, J.: Un cas de mort par surrenalité hemorrhagique, après injections massives de norvarsénobenzol, Bull. et mém. Soc. méd. d. hôp. de Paris **54**: 767 (May 16) 1938.

found to be much smaller. From the standpoint of toxicity, moreover, it is important to determine experimentally not only that animals will survive the injection of the minimum curative dose but also, by necropsy of animals so treated at varying intervals thereafter, that permanent damage to important tissues is lacking.

Since the clinical studies suggest that a curative effect depends on moderate prolonged concentration of the spirocheticidal substance in the blood, it is clear that this in turn depends on the interrelationship of dosage and time of administration. Observations on syphilis in experimental animals, while not directly transferable to syphilis in man, will nevertheless permit a more exact definition of these relationships. Such observations may show that comparable clinical results may be accomplished in a still shorter time than the apparently arbitrarily chosen five days or with a smaller and therefore perhaps safer dose than any so far arbitrarily selected.

The all important time-dose relationship should be checked not only by studies in experimental animals but also by chemical studies of excretion (already in progress) and of the concentration of the curative drug in the blood and tissues of the patient.

Nothing is known as yet of the possible effects of this method of treatment in various forms of late syphilis. It is generally thought that one reason for the less satisfactory curative results (in the biologic sense) of treatment in late as compared with that in early syphilis lies in the fact that in the late stages of the disease the organisms tend to localize in tissues which the relatively poorly diffusible trivalent arsenical drugs fail to reach in spirocheticidal concentration.

This consideration, together with the fact that in bacterial infections sulfanilamide and its derivatives owe much of their success to their extremely rapid diffusibility to all tissues of the body, suggests that the trivalent arsphenamines, which are semicolloids possessing relatively poor penetrability for tissues, presumably because they combine with serum proteins to form complexes which are either inactive or nondiffusible or both, may be much less suitable for this method of treatment than the arsenoxides, which probably do not so combine and which are therefore theoretically more readily diffusible. Indeed, it is still further suggested that other drugs much less effective than either the arsphenamines or the arsenoxides when administered by the conventional technic may prove to be superior by the new method because of the factor of greater diffusibility.

As yet, therefore, not only are the factors of dosage and proper duration of treatment unsettled, but it is not yet certain that the most suitable drug or group of drugs for this particular technic has been found.

From the immediate practical standpoint, finally, it must be emphasized that the method is one which necessitates at least one week of full hospitalization, that its dangers have not yet been accurately defined and that the patients so far reported on have been followed for an interval too short to determine the permanency of results.

While the method is therefore still in the experimental stage and unsuitable for mass application, it may nevertheless prove to be of major importance both to the individual patient and to the public. Further intensive study is amply justified.

### TRANSFUSION SYPHILIS

DeBakey and Honold [121] reemphasize the fact that syphilis is often transmitted during transfusion of blood because of lack of precautions in the selection of a donor. Frequently syphilis is so transmitted from a relative or a friend. An analysis of the reported cases of transfusion syphilis shows that the infection was usually transmitted when the donor was in the early stage of the disease, occasionally when the result of his serologic test for syphilis was negative. This view is upheld by McCluskie,[122] who reports 3 cases in which syphilis was transmitted in transfusion from donors who were clinically and serologically without evidence of such infection at the time of transfusion. All 3 of these persons presented primary lesions and positive serologic reactions shortly after serving as donors. McCluskie suggests that the risk of transfusion syphilis could be minimized by the use of blood from cadavers or, better still, by some means of rapidly destroying spirochetes in the blood withdrawn from the donor.

Such a method of destroying spirochetes in the donor's blood has recently been proposed by Kast, Peterson and Kolmer,[123] who, confirming Eagle's work as to the spirocheticidal activity of arsphenamine and neoarsphenamine in vitro, suggest the use of either drug in citrated blood to be used for transfusions. They seeded citrated blood with virulent S. pallida, added neoarsphenamine or arsphenamine in a final dilution of 1 : 20,480 and allowed the mixture to remain at room temperature for fifteen minutes. Such blood when injected into nonsyphilitic rabbits did not produce syphilis, though control animals inoculated with blood plus organisms but minus the arsphenamine become infected. The

121. DeBakey, M., and Honold, E.: Blood Transfusion: Indications, Contraindications and Complications, Internat. M. Digest **33**:301 (Nov.) 1938.

122. McCluskie, J. A. W.: The Transmission of Syphilis by Blood Transfusion, Brit. M. J. **1**:264 (Feb. 11) 1939.

123. Kast, C. C.; Peterson, C. W., and Kolmer, J. A.: The Treponemicidal Activity of Arsphenamine and Neoarsphenamine in Vitro with Special Reference to Citrated Blood and Suggested Method for the Prevention of Transfusion Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **23**:150 (March) 1939.

suggested dilution of neoarsphenamine or arsphenamine is not toxic to the recipient.

### LATE SYPHILIS

*General Considerations.*—Hasselmann [124] discusses syphilis in Arabs living between the Mediterranean Sea and the Persian Gulf. He believes that, because of racial, climatic and nutritional conditions, syphilis may manifest itself in different forms. The diseases known by various colloquial terms, such as "firjal" and "latta" in parts of Palestine, "loath" and "bejel" in the region of the Euphrates and the Tigris River valleys (Iraq and Syria), "laghout" in Lebanon, and "abou-laghif" and "jaifór" in Trans-Jordan, are, he thinks, all syphilis. Butler [125] attempts unsuccessfully to show that syphilis, yaws and bejel are one and the same disease.

*Syphilis of the Stomach.*—Carey and Ylvisaker [126] suggest that a gastroscopic examination may aid in the diagnosis of syphilis of the stomach. They review the brief literature on the subject and report on a patient whom they observed and whose stomach they examined by gastroscope. The common feature is the small gastric lumen, particularly at the antrum. The normal gastric folds are effaced, and the mucosa is atrophic. The mucosal surface is granular, and superficial ulcerations may be present. Little air can be introduced into the stomach. In their patient the stomach after antisyphilitic treatment returned to its normal appearance.

Davicovic [127] also reports on a patient with syphilis whose stomach was examined by gastroscope. There was observed diffuse thickening of the mucous membrane in the anterior pyloric region with numerous small ulcerations in this area.

*Paroxysmal Hemoglobinuria.*—Dill [128] reinvestigated latent paroxysmal hemoglobinuria. Donath-Landsteiner tests were done on 360 syphilitic patients and 160 nonsyphilitic patients who were used as controls. Latent paroxysmal hemoglobinuria as indicated by the Donath-Landsteiner test occurred only once in the 360 syphilitic patients and

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124. Hasselmann, C. M.: Syphilis Among Arabs in the Near East: Bejel and Loath in Iraq and Syria; Firjal and Latta in Palestine; Laghout in Lebanon; Abou-Laghif and Jaifór in Trans-Jordan, Arch. Dermat. & Syph. **38**:837 (Dec.) 1938.

125. Butler, C. S.: The Septic Syphilodermata, Am. J. Clin. Path. **9**:1 (Jan.) 1939.

126. Carey, J. B., and Ylvisaker, R. S.: Gastroscopic Observations of Syphilis of the Stomach, Ann. Int. Med. **12**:544 (Oct.) 1938.

127. Davicovic, S.: La syphilis gastrique, Presse méd. **47**:275 (Feb. 18) 1939.

128. Dill, L. V.: Observation on the Incidence of Latent Paroxysmal Hemoglobinuria as Evidenced by the Donath-Landsteiner Phenomenon, Am. J. Syph., Gonor. & Ven. Dis. **23**:220 (March) 1939.

not at all in the control group. The author states that, according to the literature, the incidence of latent paroxysmal hemoglobinuria has ranged from 5 to 30 per cent. In his own series the incidence was 0.025 per cent. The discrepancy, he feels, may be due to the more intensive antisyphilitic treatment now employed or to a difference in the clinical material studied.

*Juxta-Articular Nodules.*—In a detailed discussion of rheumatic subcutaneous nodules and lesions simulating them, Keil [129] points out that syphilitic juxta-articular nodules are uncommon and that many of those which occur do so as a solitary manifestation of late syphilis. There is a striking similarity of these nodules to those of rheumatic fever. They are most commonly found at the elbow, knee and hip and less commonly at the ankle, shoulder and sacrum. They are as a rule symmetrically placed, are about the size of a walnut or smaller, develop slowly and may be soft at first but with increasing age become harder. They respond to antisyphilitic therapy, disappearing in a few weeks. With ordinary staining methods there is no characteristic pathologic change in the nodules diagnostic of syphilis. The diagnosis of syphilitic juxta-articular nodule rests on (1) the association with other manifestations of syphilis, (2) the almost invariable presence of a positive serologic test for syphilis and (3) the striking response to antisyphilitic treatment.

### CARDIOVASCULAR SYPHILIS

*Incidence.*—Welty [130] has analyzed the incidence of cardiovascular syphilis in 15,000 consecutive cases in which necropsy was performed between 1927 and 1937. Cardiovascular syphilis was observed in 1,040 cases (6.93 per cent). In 192 of these the condition was aneurysm; in 216, aortic insufficiency, and in the remaining 632, simple aortitis. Seventy-four per cent of all patients were males. Sixty-eight per cent of all patients were Negroes. To demonstrate the decreasing incidence of cardiovascular syphilis over this ten year period, Welty divides his material into five groups of 3,000 autopsies each. Each group represents a period of eighteen to thirty months.

Thompson, Comeau and White [131] studied 241 patients from the standpoint of the effect of adequate and of inadequate treatment for early syphilis on the subsequent development of cardiovascular syphilis. All patients in the group had had syphilis for fifteen to twenty-five

129. Keil, H.: The Rheumatic Subcutaneous Nodules and Simulating Lesions, Medicine **17**:261 (Sept.) 1938.

130. Welty, J. W.: A Necropsy Survey of Cardiovascular Syphilis with Particular Reference to Its Decreasing Incidence, Am. J. M. Sc. **197**:782 (June) 1939.

131. Thompson, W. P.; Comeau, W. J., and White, P. D.: The Role of the Treatment of Syphilis in the Prevention of Cardiovascular Involvement, Am. Heart J. **17**:286 (March) 1939.

years. Eighteen patients (7 per cent) had definite cardiovascular syphilis and 8 (3 per cent) probable aortitis. No cardiovascular abnormalities were discovered in 190 subjects, while 25 (10 per cent) had questionable dilatation of the aorta. The patients were divided into three groups according to the amount of treatment received for early syphilis: 172 (71 per cent) had received less than twelve injection of an arsenical with equivalent heavy metal; 33 (14 per cent) had received thirteen to nineteen injections of an arsenical with equivalent heavy metal, and 36 patients (15 per cent) had received more than twenty doses of an arsenical with equivalent heavy metal. Of the 18 patients with definite cardiovascular syphilis, 17 fell into the first treatment group and 1 into the second. The authors conclude that their study supports the clinical impression that adequate treatment of early syphilis tends to prevent later clinical manifestations of cardiovascular syphilis. Blair,[132] in a general

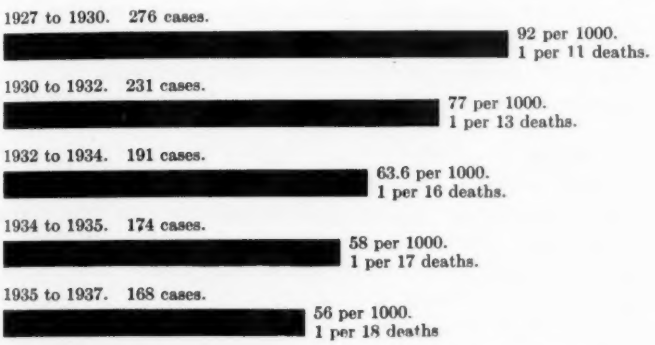


Fig. 3.—Decreasing incidence of cardiovascular syphilis at the Philadelphia General Hospital (after Welty [130]).

discussion of cardiovascular syphilis, remarks that almost none of such patients seen in his clinic has had adequate previous treatment and that a large percentage have had none.

*Gumma of the Heart.*—Diffuse gummatous myocarditis is rare. Von Haam and Ogden [133] stated that only 7 cases had been reported between 1845 and 1935. They studied the protocols of 5,213 autopsies and found that gummatous lesions of the heart had been demonstrated only in 3—in the first, isolated gummatous pericarditis; in the second, multiple gummatous myocarditis, and in the third, diffuse gummatous myocarditis and syphilitic endocarditis.

132. Blair, A.: Early Recognition of Cardiovascular Syphilis, New York State J. Med. **38**:1115 (Aug. 15) 1938.

133. Von Haam, E., and Ogden, M. A.: Syphilis of the Heart and Pericardium, Arch. Path. **26**:525 (Aug.) 1938.

Two cases of the relatively uncommon gumma of the interventricular septum are reported, one by Cossio, Vivoli and Caul [134] (remarkable for the previously unreported association of ventricular tachycardia) and the other by Coelho and d'Oliveira,[135] in which both ventricular tachycardia and ventricular fibrillation were observed.

*Aortitis.*—Herzog [136] believes the diagnosis of syphilitic aortitis may be facilitated by taking the blood pressure in both arms simultaneously. Two blood pressure cuffs are connected with a manometer by means of a Y tube. By using a symballophone, with one ear piece connected to the tubing leading to each arm, the exact time of the appearance of the beats can be determined. The blood pressure of normal persons and of those with essential hypertension are said usually to be equal in both arms. In syphilitic aortitis the pressures are often unequal.

Epstein [137] describes a method by which the aorta can be more clearly visualized on the roentgen film. The method is overpenetration, which enables one to outline regions more closely where structures are superimposed.

*Aneurysm.*—Two very interesting statistical studies of aneurysm are presented by Mills and Horton [138] and by Kampmeier.[139] Mills and Horton, working at the Mayo Clinic, analyze the observations on 596 patients with aneurysm observed in the years 1925 to 1935, inclusive, especially those relating to location of the aneurysm and the etiologic role of syphilis. The results are shown in the table. Practically all except 6 of the patients were white persons. Syphilis is rarely, if ever, a cause of intracranial aneurysm, which is usually due to embolism, congenital defect or arteriosclerosis. Likewise it is rarely the responsible factor in aneurysm of the abdominal aorta or of vessels of the extremities. Most physicians believe, however, that the presence of a thoracic aneurysm is tantamount to a diagnosis of syphilis. It is of great interest therefore that Mills and Horton could obtain no history of

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134. Cossio, P.; Vivoli, D., and Caul, H.: Syphilis of the Interventricular Septum and Ventricular Tachycardia, Am. J. M. Sc. **194**:369 (Sept.) 1937.

135. Coelho, E., and d'Oliveira, A.: Syphilis de la cloison intraventriculaire et tachycardie ventriculaire: syphilis de l'artère pulmonaire (pulmonarterite syphilitique), Arch. d. mal. du cœur **32**:17 (Jan.) 1939.

136. Herzog, F.: Simultaneous Bilateral Measurement of Blood Pressure for Diagnosis of Syphilitic Aortitis, Orvosi hetil. **82**:747 (July 30) 1938.

137. Epstein, S. H.: The Visualization of the Aorta by the Method of Roentgenographic Overpenetration, Am. J. Roentgenol. **40**:396 (Sept.) 1938.

138. Mills, J. H., and Horton, B. T.: Clinical Aspects of Aneurysm, Arch. Int. Med. **62**:949 (Dec.) 1938.

139. Kampmeier, R. H.: Saccular Aneurysm of the Thoracic Aorta: A Clinical Study of Six Hundred and Thirty-Three Cases, Ann. Int. Med. **12**:624 (Nov.) 1938.

syphilis, nor any physical or laboratory evidence of the disease, from 30 per cent of the 339 patients studied. Only 35 necropsies were performed in the series with thoracic aneurysm, and the authors provide no data as to postmortem evidence of syphilis. The average duration of life after the diagnosis of thoracic aneurysm was established was twenty and one-half months, but the authors did not relate this datum to the presence or absence of antisyphilitic treatment.

Kampmeier's paper deals exclusively with saccular aneurysm of the thoracic aorta. Of 1,113 cases data on which were available for analysis from the Charity Hospital of New Orleans and the Vanderbilt University Hospital, 633 were acceptable for study. The incidence of the clinical diagnosis of thoracic aneurysm in many large hospitals of the world is probably about 1 in 1,000 medical admissions; that of the postmortem diagnosis is probably about 1 in 100. This suggests that during life the condition is much more often missed than diagnosed. In Kamp-

*Location of Aneurysm and Incidence of Syphilis, According to Mills and Horton* [138]

| Location of Aneurysm | Cases | | Percental Incidence of Syphilis |
|---|---|---|---|
| | Number | Percentage | |
| Intracranial | 143 | 24 | 3.5 |
| Thoracic | 339 | 56.9 | 70.0 |
| Abdominal | 80 | 13.4 | 8.8 |
| Extremities | 21 | 3.5 | 9.5 |
| Miscellaneous | 13 | 2.2 | 7.7 |
| Total | 596 | 100.0 | |

meier's personal material the ratio of aneurysms to admissions was about the same for the years 1906 to 1930; but in the period 1931 to 1935, inclusive, the frequency of aneurysm decreased by more than half, suggesting that modern treatment is finally beginning to exert a preventive effect.

Kampmeier presents a more complete analysis of his cases for syphilis than do Mills and Horton. In only 289 of the 467 cases in which tests for syphilis were made were the tests positive (62 per cent); but when to this figure are added the cases in which there was a definite history of previous syphilis or of treatment for it, or other clinical, laboratory or necropsy evidence of syphilis, the incidence of syphilis rises to 81 to 84 per cent. While he does not definitely say so, Kampmeier evidently feels that the percentage of cases in which syphilis was a cause of thoracic aneurysm would have been even higher if the patients had been more carefully studied.

There is a careful analysis of the material by race, sex, age, occupation, anatomic classification, chief complaint, symptoms, physical signs,

roentgenologic evidence, cause of death, prognosis and differential diagnosis. The cause of death was definitely known in 247 cases. Death was due to rupture in 39 per cent, to respiratory obstruction in 18 per cent, to cardiac failure in 11.5 per cent, to pneumonia in 9 per cent and to scattering causes or causes unknown in the remainder.

The duration of life from the onset of symptoms to death was known in 224 cases, and was known to be three years or longer in only 18 of these. The average life expectancy was only six and four-tenths months. Unfortunately, however, Kampmeier does not relate these data to the presence or absence of treatment. It will be recalled that Padget and Moore [140] have shown that even with inadequate antisyphilitic treatment the duration of life in patients with aneurysm is prolonged to an average of thirty-two months, and in well treated patients, to an average of fifty-five months, after the development of symptoms.

Shimkin [141] collects from the literature 44 cases in which aortic aneurysm caused compression of the spinal cord, and adds 2 of his own.

Maurer [142] brings to attention that complete absence of pulsation in the radial, brachial and carotid arteries is rare. Five cases have been reported previously in which this was associated with aneurysm of the aortic arch; to these Maurer adds 2 cases in which this association was noted at necropsy at the Cincinnati General Hospital. The presenting complaint in all cases was referable to the cerebrum, evidently caused by cerebral anoxemia.

Armstrong, Coggin and Hendrickson [143] assemble 98 reported cases of spontaneous arteriovenous aneurysm of the thorax to which they add 2 cases. Prior to 1925 syphilis was mentioned as the cause of the condition in less than half of the reported cases, though since 1925 syphilis has been thought to be the cause in 77 per cent of the 26 cases described. Symptoms and signs could be analyzed in 80 cases. All patients had cyanosis, and 79 had swelling about the upper part of the thorax. The onset was sudden in 50 patients. Dyspnea on exertion was shown in 35, and 9 had orthopnea. Unconsciousness was reported in 11, severe pain in 15 and difficulty in swallowing in 6. A majority had signs of a tumor in the thorax. Occasionally a suprasternal thrill was palpable. Abnormal cardiac sounds were noted in 77 of the 80 patients; in 30 the

140. Padget, P., and Moore, J. E.: The Results of Treatment in Cardiovascular Syphilis, Am. Heart J. **10**:1017 (Dec.) 1935.

141. Shimkin, M. B.: Aneurysm of the Aorta with Compression of the Spinal Cord: Two Case Reports and Review of the Literature, Ann. Int. Med. **12**:1709 (April) 1939.

142. Maurer, E.: Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysm of the Aortic Arch, Am. Heart J. **17**:716 (June) 1939.

143. Armstrong, E. L.; Coggin, C. B., and Hendrickson, H. S.: Spontaneous Arteriovenous Aneurysms of the Thorax: A Review of the Literature with a Report of Two Cases, Arch. Int. Med. **63**:298 (Feb.) 1939.

machinery murmur of arteriovenous aneurysm was heard; in 22 there was a definite to and fro murmur. Death occurred in 54 of the 80 patients in less than one month after the onset of symptoms. Three died instantaneously. Collateral circulation was established in only 3 of the 81 patients.

Penick [144] discusses various operative methods for wiring aortic aneurysms.

*Thyrotoxicosis and Syphilitic Heart Disease.*—Among 5,000 cases of heart disease, Maher and Plice [145] found 12 cases in which syphilitic heart disease was coexistent with thyrotoxicosis. Maher and Wosika [146] have studied these 12 cases to determine what effect one condition might have on the other. In 9 of the 12 cases the thyropathy was classified as toxic adenoma and in 3 as exophthalmic goiter. Syphilitic infection antedated the development of goiter in every case. Histologic examination of the removed glands showed no evidence of syphilis. Contrary to the authors' expectation, their patients tolerated thyroidectomy remarkably well. No deaths followed operation, in spite of aortic insufficiency in 3 patients and aortic insufficiency and aneurysm in a fourth. The additional burden of thyrotoxicosis in syphilitic heart disease seemed to precipitate auricular fibrillation and congestive failure. Cure of the thyrotoxicosis relieved this burden on the heart and allowed it to return to normal rhythm and compensation. Those patients who were given antisyphilitic treatment before operation showed no cardiac improvement. Auricular fibrillation and congestive failure were uninfluenced. On the contrary, those patients who were operated on immediately showed marked improvement and no mortality.

*Effect of Warm and Cold Weather.*—Bean and Mills [147] find that coronary occlusion and congestive heart failure from arteriosclerotic and rheumatic heart disease are more common during the winter months, but that there is no such seasonal variation in congestive heart failure due to syphilitic aortic regurgitation. They believe this discrepancy to be due to the rapid progression of cardiovascular syphilis.

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144. Penick, R. M., Jr.: Technic for Wiring Aortic Aneurysms, South. M. J. **31**:1096 (Oct.) 1938.

145. Maher, C. C., and Plice, S. G.: Multiple Etiological Factors in Five Thousand Cases of Heart Disease in Chicago, Am. Heart J. **14**:490 (Oct.) 1937.

146. Maher, C. C., and Wosika, P. H.: The Combination of Thyrotoxicosis and Syphilitic Heart Disease, Urol. & Cutan. Rev. **43**:34 (Jan.) 1939.

147. Bean, W. B., and Mills, C. A.: Coronary Occlusion, Heart Failure and Environmental Temperatures, Am. Heart J. **16**:701 (Dec.) 1938. Mills, C. A., and Bean, W. B.: The Timing of Luetic Heart Failure in Relation to Heart Load, Urol. & Cutan. Rev. **43**:32 (Jan.) 1939.

NEUROSYPHILIS

*Argyll Robertson Pupil.*—Costello [148] presents a review of the literature on Adie's syndrome. He reports 2 cases and calls attention to the difficulty of differentiating the Argyll Robertson pupil of neurosyphilis from the tonic pupil of Adie's syndrome.

*Atrophy of the Optic Nerve.*—There will shortly appear jointly in the January 1940 numbers of the *American Journal of Ophthalmology* and the *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* an exhaustive review of the pathogenesis and pathologic appearance of syphilitic primary atrophy of the optic nerve.[149] This review will be followed (in the *American Journal of Ophthalmology* only) by a second review dealing with more general considerations of primary atrophy of the optic nerve and its treatment.[150] These two reviews include the literature on the subject from 1932 to the present in much greater detail than is permissible here. Reference to recent articles on atrophy of the optic nerve will therefore be omitted from this review.

*Constitutional Factors in Neurosyphilis.*—Stegmann [151] has studied from a psychiatric standpoint the family histories of 270 patients with dementia paralytica. He reports a much higher incidence of psychoses in the relatives of these patients than in those of average normal persons and believes that the majority of such patients show some evidence of mental abnormality even before infection with syphilis.

The same point is covered for tabes dorsalis by Curtius, Schlotter and Scholz,[152] who present monographically their conclusions as to this and other constitutional factors. Their study of 101 patients with this condition is of little value to the clinician. Of the 262 pages of text, 160 are devoted to a survey of constitutional and individual and familial predisposing factors and 38 to the effect of service on the development of tabes dorsalis. Only 39 pages are given to clinical considerations, and

148. Costello, M. J.: A Syndrome Simulating Tabes Dorsalis, New York State J. Med. **39**:781 (April 15) 1939.

149. Moore, J. E., and Woods, A. C.: The Pathology and Pathogenesis of Syphilitic Primary Optic Atrophy: A Critical Review, Am. J. Ophth., January 1940, to be published; Am. J. Syph., Gonor. & Ven Dis., January 1940, to be published.

150. Moore, J. E., and Woods, A. C.: Syphilitic Primary Optic Atrophy: General Considerations and the Results of Treatment by Standard Methods (Especially Subdural Treatment and Induced Fever); a Critical Review, Am. J. Ophth., 1940, to be published.

151. Stegmann, A.: Disposition und Belastung zur progressiven Paralyse, Allg. Ztschr. f. Psychiat. **108**:115, 1938.

152. Curtius, F.; Schlotter, H., and Scholz, E.: Tabes dorsalis: Klinische, erb- und konstitutionspathologische sowie sozialmedizinische Untersuchungen; unter Verwertung der Erfahrungen aus der Kriegsbeschädigten-Versorgung, in Martineck: Arbeit und Gesundheit: Sozialmedizinische Schriftenreihe aus dem Gebiete des Reichsarbeitsministeriums, Leipzig, Georg Thieme, 1938, no. 33.

no space is allotted to treatment. On the whole, the monograph might more profitably have been presented as a series of short papers in the periodical literature. The conclusions of the authors, based on an elaborate presentation of individual case histories, tables and charts, are that the various factors of human constitution which they studied play no role in the pathogenesis of tabes dorsalis, except bodily habitus, which is frequently of the asthenic type (though they fail to make it clear whether tabes develops in patients because they are asthenic or the asthenic habitus develops because of tabes), and "neuropathic constitution." By the latter term they mean that the families of tabetic patients include a higher proportion of psychiatrically unstable persons than do those of normal people. Many constitutional factors are considered in great detail, and though the results are largely negative, the work will be of value to students of this phase of medicine.

*Bladder in Neurosyphilis.*—In previous reviews (1935 to 1938, inclusive) there has been included comparatively little discussion of the newer methods of study of the bladder in neurosyphilis, the only references provided being to articles by Langworthy and his associates [153] in the reviews of 1936 and 1937, to Rubritius [154] and Muschet [155] in the review of 1937 and to Palmer and Gernon [156] and Levin [157] in that of 1938.

The subject is, however, of such increasing importance in the diagnosis and management of neurosyphilis that a more complete bibliography covering the period of these reviews is fully justified and is herewith provided.[158] The technical urologic procedure of cystometry,

153. Dees, J. E., and Langworthy, O. R.: Experimental Study of Bladder Disturbances Analagous to Those of Tabes Dorsalis, J. Urol. **34**:359 (Nov.) 1935. Langworthy, O. R.; Lewis, L. G.; Dees, J. E., and Hesser, F. H.: Clinical Study of the Control of the Bladder by the Central Nervous System, Bull. Johns Hopkins Hosp. **58**:89 (Feb.) 1936. Langworthy, O. R.; Dees, J. E., and Lewis, L. G.: Abnormalities of Micturition Due to Syphilis of the Nervous System, Am. J. Syph., Gonor. & Ven. Dis. **20**:364 (July) 1936.

154. Rubritius, H.: Die Miktionstörungen der Tabiker, Wien. klin. Wchnschr. **50**:311 (March 5) 1937.

155. Muschet, M.: Cystometric Studies: The Value of Follow-Up Examinations, Am. J. M. Sc. **192**:693 (Nov.) 1936.

156. Palmer, E., and Gernon, J. T.: The Use of Ergotamine Tartrate in the Treatment of the Tabetic Bladder, Illinois M. J. **72**:77 (July) 1937.

157. Levin, P. M.: Action of Acetyl-Beta- Methylcholine Chloride (Mecholyl) in Neurologic Disturbances of the Urinary Bladder, with a Note on the Mechanism of Spinal Shock, J. Pharmacol. & Exper. Therap. **62**:449 (April) 1938.

158. Adson, A. W.: Value of Sympathectomy in Treatment of Cord Bladder, Northwest Med. **33**:276 (Aug.) 1934. von Noszkay, A.: Zur Frage der chirurgischen Behandlung von Blasen mit verminderter Fasskraft (Kapazität) (Präsakrale Sympathikusresektion, Harnleiterverlagerung), Ztschr. f. Urol. **28**: 829, 1934. Watkins, K. H.: Clinical Value of Bladder Pressure Estimation,

*(Footnote continued on next page)*

introduced a decade or more ago, has been further studied by application not only to patients with various neurologic diseases but also to experimental animals in which various types of lesions of the spinal cord have been produced. The Baltimore group of investigators headed by Langworthy (a neurologist) and Lewis (a urologist) has been especially interested. While much remains to be done, a number of points of practical interest appear. An abnormal cystometrogram may be the earliest sign of injury to the cord in neurosyphilis, obtainable before the development of any but very minor urinary symptoms and before other objective evidence of neurologic damage can be demonstrated.

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Brit. J. Urol. **6**:104 (June) 1934. Creevy, C. D.: Neurogenic Dysfunction of the Bladder, Alterations in Physiology of Micturition Due to Lesions of the Nervous System, Arch. Neurol. & Psychiat. **34**:777 (Oct.) 1935. Deakin, R.: Clinical Demonstration (in Case of Tabetic Bladder) and Effect of Mecholyl (Acetyl-Beta-Methyl-Choline-Chloride), Urol. & Cutan. Rev. **39**:110 (Feb.) 1935. Fulcher, O. H.: Presacral (Superior Hypogastric Plexus) Neurectomy for Certain Vesical Conditions (with Especial Reference to Cord Bladder), West Virginia M. J. **31**:465 (Oct.) 1935. Gernon, J. T.; Ewert, E. E., and Herrold, R. D.: Use of Acetylbetamethylcholine Chloride in Treatment of Neurogenic Bladder and Allied Conditions: Preliminary Report, M. Rec. **141**:141 (Feb. 6) 1935. Goyanes, J., Jr.: Tratamiento quirúrgico de la disfunctión neurogénica vesical, de la enfermedad de Hirschsprung y de la dismenorrea por simpaticectomía lumbar y presacral (plexo de Hovelacque), Arch. de med., cir. y especialid. **38**: 837 (Dec. 30) 1935. Horn, K. W.: Mecholin (Acetyl-Beta-Methylcholine-Hydrochloride) in the Treatment of Certain Types of Atonic Bladder, Univ. Hosp. Bull., Ann Arbor **1**:3 (March) 1935. Lewis, L. G.; Langworthy, O. R., and Dees, J. E.: Bladder Abnormalities Due to Injury in Motor Pathways in Nervous System, J. A. M. A. **105**:2126 (Dec. 28) 1935. McCaughan, J. M., and Hershey, J. H.: Diagnosis of Neurogenic Lesions by Cystometry: Appraisal of Method Based on Experimentation with Animals, Arch. Surg. **30**:956 (June) 1935. Rose, D. K.: Cystometry, Urol. & Cutan. Rev. **39**:107 (Feb.) 1935. Creevy, C. D.: Treatment of Overflow of Neurogenic Vesical Dysfunction, J. Urol. **35**:507 (May) 1936; Minnesota Med. **19**:269 (May) 1936. Forssmann, W.: Harnverhaltung und Harnsperre, Med. Klin. **32**:1262 (Sept. 11) 1936. Gernon, J. T.; Palmer, E., and McKenna, C. M.: Recent Developments in Treatment of Neurogenic Dysfunction, Based on Cystometry, J. Urol. **35**:515 (May) 1936. Grant, F. C.: Surgery of Autonomic System of Urinary Tract (Section of Presacral Nerve or Superior Hypogastric Plexus), ibid. **36**:618 (June) 1936. Langworthy, O. R.: New Approach to Diagnosis and Treatment of Disorders of Micturition in Diseases of Nervous System, Internat. Clin. **3**:98 (Sept.) 1936. Lewis, L. G., and Dees, J. E.: Diagnosis and Treatment of Neurologic Bladder, S. Clin. North America **16**:1257 (Oct.) 1936. Muschet, M.: Diagnosis of Neurogenic Bladder by Means of Cystometer, Pennsylvania M. J. **39**:493 (April) 1936. Rose, D. K.: Present Status of Cystometry, J. A. M. A. **107**:1534 (Nov. 7) 1936. Brodie, E. L., and Phifer, I. A.: Cystometric Observations in Asymptomatic Neurosyphilis: Preliminary Report, J. Urol. **38**:419 (Oct.) 1937. Cheetham, J. G.: Presacral Neurectomy (Resection of Superior Hypogastric Plexus) for Relief of Certain Types of Bladder Dysfunction, ibid. **37**:148 (Jan.)

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The interpretation of cystometric abnormalities when neurosyphilis is otherwise asymptomatic is as yet difficult because of the fact that similar abnormalities may sometimes be found in studies of apparently healthy persons (Boyd and Smith [159]).

Since symptoms of disturbance of the bladder are, as is well known, often among the earliest signs of tabes dorsalis, a definite prognostic statement that this neurologic disease is imminently developing may sometimes be made by urologic consultation, including cystometry. Moreover, it is possible, by this procedure, to differentiate between damage to the posterior columns of the spinal cord, as in tabes, and lesions of the corticospinal tracts, as in other forms of neurosyphilis.

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1937. Creevy, C. D.: Treatment of Neurogenic Vesical Dysfunction Complicated by Lesions of Vesical Outlet, ibid. **37**:593 (April) 1937. Hortolomei, N., and Streja, M.: De l'utilité de la cystométrie, J. belge d'urol. **10**:531 (Dec.) 1937. Muschet, M.; Carp, J., and Charny, C. W.: Normal Cystometrogram, J. Urol. **37**:718 (May) 1937. Simeone, F. A., and Lampson, R. S.: Cystometric Study of Function of Urinary Bladder, Ann. Surg. **106**:413 (Sept.) 1937. Simons, I.: Cystometry: Studies in Bladder Function; Critical Review with Special Reference to Microcystometry and Sphincterometry, Brit. J. Urol. **9**:132 (June) 1937. Van Duzen, R. E.: Neurogenic Disturbances of Bladder Function, J. Urol. **37**:156 (Jan.) 1937. Adams, P. S.: Use of Cystometer in Diagnosis of Neurogenic Bladders (with Comments on Treatment and Case Reports), Nebraska M. J. **23**: (Feb.) 1932. Boyd, M. L., and Smith, W. A.: Why Are Abnormal Cystometrograms Obtained in Normal Patients? J. Urol. **40**:513 (Oct.) 1938. Cheetham, J. G.: Clinical Evaluation of Cystometer, ibid. **39**:569 (April) 1938. Gill, R. D.: Neurogenic Disturbances of Bladder: Physiology, Pathology, Symptomatology and Diagnosis, ibid. **40**:797 (Dec.) 1938. Herbst, W. P.: Treatment of Neurogenic Diseases of Bladder, ibid. **40**:789 (Dec.) 1938. ,Heusser, H.: Die Manometrie der Harnblase (Cystometrie), Ztschr. f. urol. Chir. u. Gynäk. **44**:312, 1938. Irazu, J.: Cistometría (nota previa), Rev. argent. de urol. **7**:283 (Sept.-Oct.) 1938. Kasztriner, I., and Illyés, E.: Urologic Diseases of Neurologic and Psychogenic Origin with Special Consideration of Tabetic Vesical Disorders, Gyógyászat **78**:135 (Feb. 27); 162 (March 6); 174 (March 13) 1938. Lewis, L. G., and Langworthy, O.: Cystometry, J. Urol. **40**:677 (Nov.) 1938. Magid, M. A.: Value of Cystometric Studies in Atonic Bladder, Rocky Mountain M. J. **35**:299 (April) 1938. Maitland, A. I. L.: Dysfunction of Bladder as Early Neurologic Symptom, Tr. Roy. Med.-Chir. Soc. Glasgow, 1937-1938, p. 145; in Glasgow M. J., June 1938. McLellan, F. C.: Neurogenic Bladder: Preliminary Report, Univ. Hosp. Bull., Ann Arbor **4**:43 (June) 1938. Povlsen, O.: Cystometry, Hospitalstid. supp., Festskr. Bisp. Hosp. **81**:137, 1938. Simons, I.: Cystometry: Status and Outlook, with Special Reference to Microcystometry and Sphincterometry, Urol. & Cutan. Rev. **42**:316 (May) 1938; Neurologic Studies by Means of Microcystometer and Sphincterometer: Studies in Bladder Function (Preliminary Report), J. Urol. **39**:791 (June) 1938. Brodie, E. L.; Helfert, I., and Phifer, I. A.: Cystometric Observations in Neurosyphilis, Urol. & Cutan. Rev. **43**:51 (Jan.) 1939. Rose, D. K., and Shefta, L. M.: Tabetic Bladder: Discussion of Etiology with Cystometric and Pathologic Study, South. M. J. **32**:549 (May) 1939.

159. Boyd, M. L., and Smith, W. A.: Why Are Abnormal Cystometrograms Obtained in Normal Patients? J. Urol. **40**:513 (Oct.) 1938.

Particularly important is the fact that by this technic a competent urologist is often able to define clearly to what extent urinary symptoms in a neurosyphilitic patient are due to partial obstruction or to damage to the innervation of the musculature of the bladder.

Finally, cystometry is of value in determining the proper method of treatment, e. g., whether one should employ acetylbetamethylcholine hydrochloride (mecholyl) as a parasympathetic stimulant, atropine as a parasympathetic depressant or presacral sympathectomy.

In our own practice (working with Lewis and Langworthy) cystometric study of the frequency of appearance of urinary retention, partial or complete, during treatment of apparently uncomplicated dementia paralytica by induced fever has brought out the fact that involvement of the spinal cord (i. e., the tabetic form of dementia paralytica) must be far more common than is usually suspected.

The practical value of cystometry, while perhaps familiar enough to neurologists and urologists, has apparently not yet received the attention it deserves from internists and syphilologists.

*Pathology of Dementia Paralytica.*—In an excellent article Galbraith [160] reviews the pathology of dementia paralytica. He concludes:

> . . . the histopathological conception of general paralysis . . . has been considerably extended. Notable additions to our knowledge of the morphological aspect of the process have been created by the discovery of the iron reaction, by the finer and more selective methods of demonstrating the glial elements, . . . and by further studies of atypical forms of the process. . . .
>
> In . . . general paralysis there are many problems awaiting our attention. . . . Although general paralysis may be one of the best known diseases from the histologic aspect, yet . . . the origin of the psychologic manifestations, apart from the gross dementia due to cortical destruction in the later stages, is as obscure as in the functional psychoses. The exact circumstances of the invasion of the nervous parenchyma have yet to be elucidated, and it is unknown what factor is responsible for the breach in the "hæmato-encephalic" barrier. Further, we have no explanation . . . for the constant and characteristic distribution of the disease process. . . . the *rôle* of the spirochæte [in the development of certain pathologic changes] has been neither satisfactorily assessed nor eliminated. [Nor has it been explained] why it eludes demonstration in certain cases where there is other undoubted evidence of an active stage of the disease. The exact nature of the iron reaction, which is evidently unknown in other organs affected by syphilis, also merits considerable attention.
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> . . . The possibilities of purely histologic research are by no means exhausted, and there is yet much scope in the direction of thorough and systematic examinations of the entire nervous system, . . . . Finally . . . the most promising avenue will eventually prove to be the co-operation of the histologist and the bacteriologist in . . . experimental studies upon the spirochæte.

160. Galbraith, A. J.: Some Problems in the Histo-Pathology of General Paralysis of the Insane, Brit. J. Ven. Dis. **14**:197 (July) 1938.

*Treatment of Neurosyphilis.*—(*a*) Tabes Dorsalis. In a paper important both for the large number of patients studied and for the statistical details, O'Leary and the Cooperative Clinical Group [161] have analyzed the outcome of treatment in 985 patients with tabes dorsalis. They summarize their conclusions as follows:

*Diagnosis.*—(a) Blood. Thirty-two percent of the patients with tabes dorsalis had a negative blood Wassermann reaction and a positive spinal fluid at the time the diagnosis was made. When the blood Wassermann reverses to negative the likelihood of clinical improvement is greater than when the Wassermann remains positive, and clinical progression is more likely if the serology is constantly positive. A relapse of the blood Wassermann from negative to positive is accompanied by a similar relapse of the spinal fluid in 29 percent of the cases. The blood Wassermann reaction is an inefficient guide in the treatment of tabes dorsalis.

(b) Spinal fluid. The degree of abnormality of the spinal fluid indicates with a fair degree of accuracy the prognosis and in addition serves as a guide in estimating in advance the intensity, duration, and type of treatment indicated. Spinal fluids with the milder degrees of abnormality respond more satisfactorily, more quickly, and more permanently than do those with the severe grades of positivity. Treatment failures, as evidenced by clinical progressions, were more common in the cases with severe degrees of spinal fluid involvement. Clinical arrest may occur even though the spinal fluid remains positive, and, on the other hand clinical progression may continue in the presence of completely negative blood and spinal fluid reports. Nevertheless the best results were noted in the majority of patients who obtained complete serologic reversals to negative.

(c) Blood versus spinal fluid. Of the tabetics who had never been treated for syphilis, 31 per cent had a negative blood and a positive spinal fluid reaction at the time of the original examination. In 5 percent of the tabetics not previously treated for syphilis, both the blood and spinal fluid were completely negative. A spinal fluid that vacillates between negative and positive offers a better prognosis than a spinal fluid that remains persistently positive, because in this latter group clinical progression developed in one-quarter of the cases. When the blood and spinal fluid were both reversed, 38 per cent showed symptomatic recovery; when the spinal fluid reversed and the blood was unchanged clinical arrest occurred in 24 percent; when the spinal fluid remained positive and the blood serologic reactions became negative symptomatic recovery was noted in 17 percent; and when both blood and spinal fluid remained positive clinical recovery was noted in 15 percent. A study of clinical progression showed that when the blood and spinal fluid remained positive 20 percent progressed and that when both tests were completely negative only 3 per cent developed advanced signs of the disease.

*Treatment.*—(a) Serology. An accurate comparative appraisal of the numerical value of routine treatment, intraspinal treatment, malaria therapy, and tryparsamide was not feasible in this material; some pertinent facts, however, were elicited about the four therapeutic procedures. The treatment of tabes must be individualized because in certain patients excellent results are obtainable after a few

161. O'Leary, P. A.; Cole, H. N.; Moore, J. E.; Stokes, J. H.; Wile, U. J.; Parran, T.; Vonderlehr, R. A., and Usilton, L. J.: Tabes Dorsalis: Cooperative Clinical Studies in the Treatment of Syphilis, Ven. Dis. Inform. **19**:367 (Nov.) 1938.

injections of arsphenamine and a heavy metal. In others the intensive use of chemotherapy and perhaps the addition of one or two of the supplemental measures is necessary to arrest the process, while in some patients the intensive and prolonged use of the specific as well as the nonspecific methods will fail to control the disease.

In 60 percent of a group of 266 patients who received only routine treatment the spinal fluid became negative. However, of the 396 patients who were started on routine treatment in only 29 percent was the spinal fluid reversed, and of the group in whom reversal failed to occur 173 were given intraspinal therapy which was followed by serologic negativity in 53 percent. In other words, intraspinal therapy was successful in reversing the spinal fluid in more than one-half of those in whom routine treatment failed. In another group of 66 patients tryparsamide was successful in reversing the spinal fluids in 29 percent after routine and intraspinal therapy had failed. Malaria therapy was given to 75 patients after the other supplemental methods had failed and in 35 percent of these the serology was reversed to negative. The value of the supplemental methods is further demonstrated by the fact that in 194 patients who failed to obtain serologic reversal from routine treatment the auxiliary measures were serologically successful in 51 percent. The majority of the reversals occur by the third year of treatment with the various treatment procedures with the exception of tryparsamide with which the maximum results are noted about the tenth year. If toward the end of the first year of treatment or after 20 injections of arsphenamine and twice as much heavy metal have been given and the spinal fluid is unchanged, the supplemental treatments should be given, bearing in mind that intraspinal therapy will produce serologic reversals in about one-half the time that tryparsamide requires, and furthermore that malaria therapy will reverse the serology in one-third of the cases in which routine intraspinal therapy and tryparsamide have failed.

(b) Clinical results. The best clinical results were noted in those patients in whom the manifestations of tabes were of recent appearance, in whom the syphilis was of less than 10 years' duration, and who obtained reversals of the blood and spinal fluid to negative. The less abnormal the spinal fluid the better were the clinical results, and to obtain successful results from routine treatment more than 20 injections of arsphenamine and twice as much heavy metal should be given. Of the 286 patients who received only routine treatment clinical arrest appeared in 15.4 percent; while in 25 percent of 281 patients who did not show a definite clinical improvement on routine treatment the use of intraspinal therapy produced clinical arrest. Tryparsamide under similar circumstances produced decided clinical improvement in 26 percent, and malaria therapy was likewise successful in 20.5 percent. When a study was made of the influence of the various schemes of treatment on clinical progression it was found that in a group of tabetics who were receiving various types of treatment clinical progressions appeared in 30 percent; when intraspinal therapy was added the incidence of clinical progressions dropped to 8 percent. Malaria decreased progressions from 16 percent to 11 percent and tryparsamide did not exert any material influence in this regard.

Clinical progressions were noted in 14 percent (139) of the entire group of 968 tabetics. Advanced forms of tabes dorsalis, general paralysis, taboparesis, and vascular neurosyphilis were the most common types of progression noted. In those who had the Group III type of spinal fluid the majority of the clinical progressions were to general paralysis, while in most of those who had the Group

II type of fluid advanced signs of tabes dorsalis developed. In 15 percent of the patients who had a negative spinal fluid at the time the diagnosis of tabes was made clinical progressions occurred.

In this material the clinical response was usually preceded by the serologic reversal; however, the proportion of cases which obtain neither a clinical nor serologic response increases with the severity of involvement of the spinal fluid. Although clinical arrest was accompanied by serologic reversal in 70 percent it is to be noted that clinical progression may also appear in the presence of spinal fluid negativity. In 13 percent who did not obtain serologic reversal clinical arrest was noted; hence spinal fluid findings in tabes dorsalis do not always parallel the clinical outcome of the case.

*Symptomatology.*—The outstanding observations made on the influence of the various treatment methods on the symptoms of tabes may be briefly summarized as follows: In 13 percent of the patients with optic atrophy the vision was improved and in 36 percent the progressive loss of vision was stopped. Malaria therapy was more successful than the other therapeutic measures in controlling optic atrophy after the patients had been given moderate amounts of chemotherapy.

Charcot's joints were improved in 7 percent and arrest of the process was noted in 56 percent; none of the systems of treatment demonstrated any marked superiority in this manifestation of tabes. Twenty percent of the patients with Charcot's joints had negative blood and spinal fluid reactions.

Trophic ulcers were completely healed in 47 percent, with no outstanding benefit from any therapeutic measure.

Ataxia disappeared in 15 percent of the cases and in 41 percent it was materially improved, and although the results were about the same from the four methods of treatment there were fewer cases that showed an advance in the ataxia following intraspinal therapy.

The neuritic pains were the most frequent symptoms of tabes and they were completely overcome in 31 per cent of the cases, while in 35 percent the severity and frequency of the pains were lessened. Routine treatment alone had a higher percentage of successful results than did any of the supplemental measures in that 32 percent of the patients had a complete disappearance of the pains following this type of treatment. Malaria therapy was the least successful in the control of this symptom due no doubt to the fact that it was employed in the cases in which the other methods had given no relief.

Gastric crises disappeared following treatment in 44 percent and were less severe in 25 percent. Routine treatment was again the most successful method of treatment.

Incontinence disappeared in 24 percent, while in 38 percent the complaint was improved. Malaria therapy was most successful in the control of this complication.

Diplopia was the most responsive symptom to treatment, as it disappeared in 83 percent of the cases and in the majority of the cases from routine treatment.

It will not be possible to estimate accurately the value of any specific or nonspecific therapeutic program for tabes dorsalis until the incidence of cases is known in which the symptoms of the disease disappear spontaneously as well as those that progress to the end point. A study of the influence of treatment on the objective signs of the disease was not attempted.

Metildi,[29] aware of the fact that the cause of lightning pains in tabes dorsalis is unknown and that the lesion of the spinal cord is similar to one which may be produced in swine by a diet deficient in vitamin $B_1$, treated

6 patients suffering from the lightning pains of tabes dorsalis with thiamin chloride. From 10 to 20 mg. of this substance was given intravenously at weekly intervals. There was definite symptomatic improvement in all.

Reese and Hodgson,[162] in order to throw some light on the relationship of tabes dorsalis and vitamin $B_1$, have studied the blood, analyzed the gastric contents and determined the pyruvic acid on a group of patients with neurosyphilis. The incidence of achlorhydria in 168 patients with neurosyphilis was no greater than in nonsyphilitic patients of corresponding age groups. Studies of the blood and determinations of pyruvic acid were made on all neurosyphilitic patients who had achlorhydria. Their blood was normal, and the pyruvic acid levels were not significantly altered. In short, the authors were unable to demonstrate vitamin B deficiency in tabes dorsalis. However, they treated a group of tabetic patients with liver extract, vitamin $B_1$ and yeast and observed marked symptomatic improvement. These patients were not given antisyphilitic treatment. Ataxia diminished, sensory disturbances were symptomatically improved, and in 1 instance there was an increase in the size of the visual fields. The authors suggest that a partial explanation for involvement of the central nervous system in syphilis may be a deficiency of vitamin $B_1$ and that if the patient is saturated with this vitamin, the normal resistance of the tissues will return, thereby preventing further attack by S. pallida.

(*b*) Dementia Paralytica. Many articles continue to appear in the literature dealing with the late results of the treatment of dementia paralytica with malaria and with fever mechanically induced. The following references are representative.

Escher [163] reexamined 155 of 296 patients with this disease who were treated with malaria from 1922 to 1934. Sixteen were fully recovered, 81 improved and 58 unimproved. Vervaeck [164] investigated the status of 83 such patients who had received malaria treatment ten years previously. The final outcome was favorable in 36 per cent. Taddei [165] reexamined 260 of 298 patients with dementia paralytica who had been followed for eleven years. He found 39 per cent cured, 26 per cent partially cured, 5 per cent unimproved and 14 per cent dead of the dis-

162. Reese, H. H., and Hodgson, E. R.: Tabes Dorsalis and Vitamin B Deficiency, Urol. & Cutan. Rev. **43**:56 (Jan.) 1939.

163. Escher, F.: Nachuntersuchungen der in der Heilanstalt Burghölzli-Zürich von 1922-1934 mit Malaria behandelten Paralytikar, Schweiz. Arch. f. Neurol. u. Psychiat. **42**:37, 1938.

164. Vervaeck, P.: Les chances de survie et de guérison des paralytiques généraux (80 catamnèses dix ans après la malariasation), J. belge de neurol. et de psychiat. **38**:508 (July) 1938.

165. Taddei, G.: Gliesite della paralisi progressiva curata con la malaria: Statistica dell instituto psichiatrico di Firenze, Riv. di pat. nerv. **51**:503 (May-June) 1938.

case. Van der Heide [166] analyzed the results in 274 patients treated with malaria. One fourth of the group had a complete recovery sustained over several years. The results were better in early dementia paralytica and in the expansive manic form. Huskisson [167] presents the results in 300 patients treated with tertian malaria; 17 per cent recovered, 40 per cent improved, 30 per cent were not changed and 12 per cent died. Williams [168] says that of the patients with dementia paralytica treated at the Indiana State Hospital during the fiscal year 1937-1938, 30 to 33 per cent improved, 30 to 40 per cent did not improve and 28 to 38 per cent died. Only about 12 per cent of the group could be discharged from the hospital.

(*c*) Gumma of the Brain. Alpers [169] reports 3 cases of solitary gumma of the brain. There are no characteristic signs or symptoms except those of a tumor of the brain, and treatment is primarily surgical. Antisyphilitic treatment should, Alpers thinks, be delayed until after operation.

(*d*) Combined Fever and Chemotherapy in the Treatment of Neurosyphilis. Bennett and Lewis [170] present data to show the superiority of a combination of fever and chemotherapy for neurosyphilis over either alone. Mapharsen or bismarsen (number of doses not stated) was given during the height of mechanically induced fever. Of 10 patients with late asymptomatic neurosyphilis, strongly positive findings in the cerebrospinal fluid were completely reversed in 7, partially reversed in 2 and unchanged in 1. Of 19 patients with dementia paralytica, complete remission with full occupational recovery followed in 14, moderate improvement in 3 and no improvement in 2. Of 31 patients with tabes dorsalis of the most severe type, many with resistant chronic symptoms, 16 (52 per cent) had complete relief of all predominating symptoms; 11 (35 per cent) had improvement in all predominating symptoms with disappearance of some of them, while only 4 were unimproved. Of 28 patients with neuritic pains, 24 were definitely benefited or relieved. Eleven of 15 patients with gastric crises were completely or partially

166. van der Heide, C.: Malarial Therapy of General Paralysis, Nederl. tijdschr. v. geneesk. **82**:3331 (July 2) 1938.

167. Huskisson, D. S.: Malarial Pyrotherapy for Syphilitic Disease of Central Nervous System, South African M. J. **12**:589 (Aug. 29) 1938.

168. Williams, C. L.: Neurosyphilis, J. Indiana M. A. **32**:62 (Feb.)1939.

169. Alpers, B. J.: Gumma of the Brain, Am. J. Syph., Gonor. & Ven. Dis. **23**: 233 (March) 1939.

170. Bennett, A. E., and Lewis, M. D.: The Prevention and Treatment of Neurosyphilis by Combined Artificial Fever and Chemotherapy, with Report of Results in Seventy-Two Cases, Nebraska M. J. **23**:295 (Aug.) 1938; The Prevention and Treatment of Neurosyphilis by Combined Artificial Fever and Chemotherapy, Am. J. Syph., Gonor. & Ven. Dis. **22**:593 (Sept.) 1938.

relieved. Of 12 patients with severe, disabling types of meningovascular neurosyphilis, complete relief from predominating symptoms was secured in 10.

These results are so far superior to any reported by other workers from fever therapy or chemotherapy alone, and are so in line with the experimental data now beginning to appear, e. g., from Borchers,[26] as to suggest that further clinical and experimental studies in this important therapeutic field are urgently needed.

(*e*) Aldarsone. Kamman [171] reports the use of aldarsone, a new pentavalent arsenical (formaldehyde sulfoxylate of 3-amino-4-hydroxyphenylarsonic acid), in the treatment of 53 patients with neurosyphilis. The drug was found to be relatively nontoxic. Kamman feels that the drug is an effective agent in the treatment of neurosyphilis.

(*f*) Malaria. Milam and Kusch [172] have treated 29 white and 6 Negro patients with Plasmodium knowlesi, the malarial parasite responsible for spontaneous malaria in apes. All of the white patients were susceptible to the organism, but none of the Negroes responded. The infection was at times quite heavy, more than 1 per cent of the red blood cells being parasitized. Relapses were not infrequent.

Sioli, Kentenich and Boldt [173] describe in detail the technic for the cultivation of mosquitoes (Anopheles) to be used in the malarial treatment of dementia paralytica. They have collected 27 different swarms of mosquitoes in the past three years, all of which successfully transmit malaria to human beings.

Mayne and Young [174] combined Plasmodium vivax and Plasmodium malariae in the treatment of 16 patients suffering from dementia paralytica. They observed that one of the strains became predominant, the other tending to disappear. The predominant species was not the same in every instance, but was usually the tertian. It is probable that the predominance of one strain over the other is not due to cross immunity.

Boyd, Kitchen and Matthews [175] have demonstrated that there is no cross immunity between P. vivax and Plasmodium falciparum. They

171. Kamman, G. R.: Intravenous Aldarsone in the Treatment of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **22**:638 (Sept.) 1938.

172. Milam, D. F., and Kusch, E.: Observation on Plasmodium Knowlesi Malaria in General Paresis, South. M. J. **31**:947 (Aug.) 1938.

173. Sioli, F.; Kentenich, A., and Boldt, E.: Weitere Erfahrungen über die Zucht der Anopheles und ihre Verwendung in der Malariabehandlung der Paralytiker, Arch. f. Schiffs- u. Tropen-Hyg. **43**:1 (Jan.) 1939.

174. Mayne, B., and Young, M. D.: Antagonism Between Species of Malaria Parasites in Induced Mixed Infections: Preliminary Note, Pub. Health Rep. **53**: 1289 (July 29) 1938.

175. Boyd, M. F.; Kitchen, S. F., and Matthews, C. B.: Consecutive Inoculations with Plasmodium Vivax and Plasmodium Falciparum, Am. J. Trop. Med. **19**:141 (March) 1939.

inoculated patients with either P. vivax or P. falciparum and subsequently, during the incubation period, the period of acute attack or after recovery, inoculated them with the heterologous species. Inoculation with the heterologous strain during the acute attack or after recovery was successful in every instance. Inoculation with the heterologous species during the incubation period, however, gave negative results in 2 instances. The authors are unable to explain this observation but believe that it is not the result of antagonism between the two species. They feel that if there was antagonism, all superinfections with the heterologous strain should have been negative.

Goldman [176] reports the use of mapharsen in the treatment of 24 patients suffering from tertian malaria. One patient had spontaneous malaria; the remaining 23, malaria inoculata. The dose of mapharsen was 0.04 to 0.06 Gm. Fourteen patients received a single injection, 1 received four injections and 9 each received eleven injections. There were two recurrences, both in patients receiving one injection, and both responded to further treatment with mapharsen. The author believes that mapharsen has a definite place in the treatment of tertian malaria.

(*g*) Lumbar Puncture. In order to investigate the effect of lumbar puncture on the cerebrospinal fluid, Scheid [177] performed puncture and repuncture on 106 persons, 18 of whom had no clinical manifestations of disease of the central nervous system. In the cerebrospinal fluid of 16 of the 18 normal persons there was an increase in lymphocytes at the time of the second puncture (two to four days after the first puncture) but no change in total protein, globulin, sugar or mastic reaction. Cerebrospinal fluid which was abnormal at the time of the first puncture showed a less marked increase in lymphocytes and a slight decrease in total protein, globulin, sugar and mastic reaction at the time of the second.

### SYPHILIS AND PREGNANCY

*Incidence of Syphilis in Pregnant Women and Stillborn Infants.*—Harrington and Matschat [178] show that there has been a significant decrease in the incidence of syphilis in pregnant women in a large New York Clinic during the period from 1914 to 1937. Of 5,500 women examined before September 1923, 7.58 per cent had positive routine serologic tests for syphilis; of 4,422 examined from 1923 to 1937, only 4.36 per cent had positive tests.

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176. Goldman, D.: The Use of Mapharsen in the Treatment of Malaria, Am. J. M. Sc. **196**:502 (Oct.) 1938.

177. Scheid, W.: Ueber Liquorveränderungen nach der Lumbalpunktion, zugleich ein Beitrag zur Frage der postpunktionellen Symptome, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:397, 1938.

178. Harrington, H., and Matschat, L. J.: Syphilis in Dependent Mothers, Am. J. Syph., Gonor. & Ven. Dis. **22**:513 (July) 1938.

Montgomery [179] investigated the cause of 449 stillbirths in Philadelphia. Syphilis was found to be the cause of 24 (9 per cent). Twenty of these could have been prevented. Of 49 instances in which the cause of stillbirth was unknown, serologic tests were done on the mother in only 15.

*Placental Transmission of Arsenic.*—Various workers have shown that after the administration of an arsenical to a pregnant woman or animal the drug can be readily demonstrated in the placenta, particularly the fetal portion, but is present only in minute quantities in the blood and organs of the fetus. Snyder and Speert [180] have investigated further the transmission of arsenic to the fetus. They gave single injections of neoarsphenamine to rabbits in different stages of pregnancy and calculated the arsenic present in the fetus and in the placenta. Arsenic could not be demonstrated in the fetus until the beginning of the latter half of pregnancy. The placenta contained eighteen times as much arsenic as the fetus, and the fetal portion of the placenta contained six times as much arsenic as the maternal portion. Two conclusions drawn by the authors were:

> Variations in the arsenic content of the placentas could not be correlated with the stage of pregnancy.
>
> The concentration of arsenic in the fetus near term approaches the level calculated to be present in the maternal tissues when definite antisyphilitic effect is exerted.

*Treatment.*—Costello and associates [181] analyzed the outcome of pregnancy in 116 syphilitic mothers treated with mapharsen. Bismuth preparations were given to these patients concurrently. These women gave birth to 106 (91.4 per cent) living infants. Of 72 women who received six or more treatments, 94.7 per cent had living children. Of the 106 babies born alive, 50 were followed in the pediatric clinic, and 5 (10 per cent) of these had positive results from the Wassermann test. The authors then compare the results obtained with mapharsen with those obtained with a bismuth preparation alone, with neoarsphenamine and with acetylarsan (p-oxyacetylaminophenylarsinate of diethylamine). They find that fewer syphilitic children are born alive after treatment with neoarsphenamine than after treatment with mapharsen plus a

179. Montgomery, T. L.: Problems in the Etiology and Prevention of Stillbirths, Am. J. Obst. & Gynec. **36**:975 (Dec.) 1938.

180. Snyder, F. F., and Speert, H.: The Placental Transmission of Neoarsphenamine in Relation to the Stage of Pregnancy, with Special Reference to the Prenatal Treatment of Syphilis, Am. J. Obst. & Gynec. **36**:579 (Oct.) 1938.

181. Costello, M. A.; Coppolino, J. A.; Rakoff, A. E.; Roeder, P. H., and Dickson, G. S.: Mapharsen in the Treatment of Syphilis Complicating Pregnancy: A Comparative Study, Am. J. Syph., Gonor. & Ven. Dis. **23**:332 (May) 1939.

bismuth preparation or with acetylarsan. The percentages, in the order of the drugs named, are 3.2, 10.07 and 38.4.

In evaluating these drugs in terms of living births, they find that after six or more doses, respectively, of quinine bismuth iodide, mapharsen plus bismuth, acetylarsan and neoarsphenamine the percentages of living children are, in the order of drugs named, 80, 94.4, 96.5 and 96.7. A control series of 65 untreated mothers had only 69.1 per cent living children.

### CONGENITAL SYPHILIS

*Pathologic Observations.*—Orsós [182] describes what he believes to be the first case of syphilitic changes in a 4 week old embryo to be reported. A 17 year old girl under treatment for secondary syphilis aborted. In the aborted material was found a 4 week old embryo. Sections of the embryo revealed a pathologic change of an inflammatory nature in the region where the neck would later develop. In spite of the fact that no S. pallida could be demonstrated in this lesion, the author assumes that it was due to syphilis.

Carnevale Ricci [183] examined histopathologically the ears of 43 congenitally syphilitic infants. Some were stillborn at term, and others died a few days to two months after birth. He found definite syphilitic changes in the ears of 8 of the 43 infants examined. Syphilitic lesions of all degrees of severity and in all stages of development were found in all parts of the ear. The labyrinth was most commonly affected, and both the bony and the membranous capsule were involved. The aural lesions were generally associated with severe syphilitic changes in other parts of the body and many of the infants had syphilitic meningitis. There are excellent photomicrographs, including several colored plates.

D'Aunoy and Pearson [184] were able to find congenital syphilitic lesions of the intestine in 3 (1.3 per cent) of 230 children with congenital syphilis who were examined post mortem. In each instance S. pallida was demonstrated in the lesions. The authors conclude from their personal experience and from a review of the literature that more than 75 per cent of congenital syphilitic intestinal lesions are in stillborn infants and children who live less than twenty-four hours. The most characteristic intestinal lesion is a raised yellow plaquelike band encircling the bowel, which is usually found in the lower portion of the ileum. There is necrosis of the mucosa and submucosa. When spirochetes are

182. Orsós, I. J.: Syphilitische Veränderungen an vierwöchigem Embryo, Arch. f. Dermat. u. Syph. **178**:188, 1938.

183. Carnevale Ricci, F.: Osservazioni istopatologiche sulle sifilide congenita dell'orecchio, Arch. ital. di otol. **50**:521 (Oct.) 1938.

184. D'Aunoy, R., and Pearson, B.: Intestinal Lesions in Congenital Syphilis: Histologic Study with Report of Three Additional Cases, in All of Which Spirochetes Were Identified, Arch. Path. **27**:239 (Feb.) 1939.

found, they are most prominent in the perivascular tissue and in the walls of the blood vessels. If present in the muscle coats, they tend to lie in the direction of the muscle fibers.

*Diagnosis.*—In a paper which is notable for clear thinking and calm presentation of a subject which too frequently previously has inspired other authors to the contrary, Black [185] considers the criteria on which a diagnosis of congenital syphilis properly should be based. In the days before antisyphilitic treatment of pregnant women with syphilis was general, congenital syphilis was both common and severe in the infants born of these women. At present, however, many pregnant syphilitic women have had some prepartum care, which may have prevented or may have "cured" fetal infection. In some instances, however, it has served only to suppress the manifestations of syphilis in the newborn.

Black says, therefore:

> The diagnosis of congenital syphilis, once concerned principally with severe and relatively easily recognized cases, has been rendered much more difficult as a result of the nearly universal use of ante-partum treatment in infected women. A more refined and judicious use of diagnostic methods is necessary now in order to identify the occasional mildly infected infant among the many syphilis-like babies born of treated syphilitic mothers. Coincident with the diminished frequency and severity of congenital syphilis, there must come a change in attitude toward the newborn babies of syphilitic women. Whereas previously the baby was properly considered probably syphilitic, now the infant may be regarded as nonsyphilitic until proved otherwise. At one time it was perhaps excusable to give antisyphilitic treatment to all babies born of syphilitic women; only the exceptional infant was unjustly exposed to the dangers and disadvantages of unnecessary treatment. Such an attitude now would be an injustice to most of the babies. . . .
>
> There are three main methods of investigation by which the unquestionable presence or absence of congenital syphilis in living infants or children may be definitely determined:
>
> (1) bacteriologic examination
>
> (2) serologic examination
>
> (3) roentgenologic osseous examination.

By the term "bacteriologic examination," the author means a search for S. pallida by dark field examination of material from the umbilical vein and from "suspicion arousing" lesions or abnormalities, such as failure of the umbilical stump to heal.

As to serologic examination, the author states:

> . . . There is overwhelming evidence that . . . reagin may be present in the circulating blood of newborn infants born of syphilitic mothers without the concomitant presence of spirochetes in the infant's tissues. Presumably the

185. Black, W. C.: Diagnosis of Congenital Syphilis: Pathognomonic Criteria, J. Pediat. **14**:761 (June) 1939.

reagin, . . . crosses the placental barrier from the maternal to the fetal blood. Thus a nonsyphilitic newborn infant may have a positive blood [serologic] test. . . .

In the asymptomatic syphilitic infant reagin may be entirely absent at birth, but it will be present within a few weeks or at most within four months. More commonly the first serologic test will be positive. The reagin responsible for this early positive test may be either maternal or fetal in origin or may be a mixture of both. . . . In general, titers tend to be higher in infected than in uninfected infants. If the cord blood reagin titer exceeds by a wide margin the maternal level, one cannot escape . . . the probability that the infant is syphilitic. There is as yet not enough clinical support to consider this observation of pathognomonic significance. Serologic differentiation between the infected and noninfected newborn infants depends, in our present state of knowledge, upon an increase in the amount of the reagin in the infected baby.

Roentgenologic findings, in the very nature of the case, are a much less direct evidence of the presence of a disease such as syphilis than is the identification of the causative organism or a specific serologic reaction. Considering the recent confusion caused by the deposition of bismuth lines in the long bones of infants whose mothers have been treated with a preparation of this metal during pregnancy, Black recognizes the present unsettled state of roentgenologic diagnosis. However, from his study of 102 cases of congenital syphilis, among which, judged by a mortality rate of 42 per cent, the average intensity of infection was great, he lists ten types of roentgenologic osseous change which he considered diagnostic of congenital syphilis:

1. Well-defined saw-tooth metaphysis in well calcified bones
2. Deep zones (in the longitudinal axis) of submetaphyseal rarefaction
3. Multiple "separation of epiphyses" with or without impaction in bones which are not rachitic
4. Bilateral symmetrical osteomyelitis of the proximal mesial aspects of the tibiae
5. Multiple circumscribed osteomyelitis of the long bones shown by the roentgen rays as patchy areas of rarefaction
6. Multiple longitudinal areas of rarefaction (osteomyelitis) in the shafts of the long bones, sometimes resulting in fractures
7. Destructive lesions at the mesial or lateral aspects of the metaphyses (foci of rarefaction)
8. Multiple areas of cortical destruction generally seen within a centimeter of the ends of the bones
9. Double zone of rarefaction at ends of bones
10. Localized periosteal cloaking occurring in more than one bone.

He feels that criteria 1, 3, 4, 5, 6, 7 and 8 are still acceptable as pathognomonic. As he points out, however, a very high degree of technical perfection in the roentgenogram is necessary for unequivocal demonstration of criterion 1. In criterion 7 the changes should be multiple and very definite.

There is perhaps some question as to whether criteria 2, 9 and 10 are sufficiently reliable to retain their pathognomonic significance. As for criterion 2 we feel, . . . that perhaps it should not be included in its present form as a sign by which a definite diagnosis of congenital syphilis can be made. . . .

Black presents a schema of diagnosis, the use of which he feels will establish the presence or absence of syphilis in nearly all babies within three weeks after birth. Although he grants that there are perhaps occasional instances in which one would be justified in beginning treatment for syphilis in infancy without the support of an absolutely positive diagnosis, he holds that such action should be taken only after consultation with the best available authority in each of the fields concerned and that a sharp distinction should be drawn between a positive and a presumptive diagnosis. The procedure for the diagnosis of congenital syphilis in young infants was described by Black as follows:

1. Routine Wassermann test, history (with syphilis in mind), and careful physical examination (with syphilis in mind) of all pregnant women at the time pregnancy is diagnosed. Frequent check-ups of suspicious cases.

2. Suitable treatment of every pregnant woman who has or has had syphilis, regardless of the results of serologic tests, physical signs of the disease, or previous treatment.

3. Dark-field examination of umbilical vein scrapings in every case in which there has been inadequate, irregular, or no ante-partum treatment.

4. Cord or peripheral infant blood Wassermann or other serologic test in every case and titrations in all positive cases. Without this original test, titrated when positive, it is impossible to evaluate properly the next test.

5. Roentgenograms of the long bones within two weeks after birth of those infants in which the presence of syphilis is fairly probable (inadequate, irregular or no ante-partum treatment) or in which the first serologic reaction was positive.

6. Repeated infant blood Wassermann tests at not longer than two-week intervals with titrations in cases in which the original test was positive.

7. Repeated roentgenograms at one month or six weeks of age in cases in which the diagnosis is still in doubt.

8. Repeated dark-field examinations of any suspicious lesions (mucous membranes of nose, mouth, or anus; diaper rash; slowly healing umbilical stump etc.).

9. Spinal fluid examinations of infants in whom the presence of syphilis is fairly probable (see 5 above) when subsequent examinations have not revealed positive diagnostic results.

*Congenital Syphilis as a Starting Point for Case Finding.*—In a discussion on the management of syphilis in pregnancy and the diagnosis of early congenital syphilis, Davis [186] calls particular attention to the importance of family case finding. In examining the families of 1,676 syphilitic mothers registered with the New York City Health

186. Davis, M. L.: Prevention of Congenital Syphilis, Arch. Pediat. **55**:590 (Oct.) 1938.

Department, she found 30 per cent of the persons examined to be infected. In two families alone, 13 of 16 living members examined had syphilis!

*Congenital Syphilis in One of Twins.*—Wile and Welton [187] present a review of the literature on syphilis in twins and report a thoroughly studied case of prenatal syphilis in one of fraternal twins.

*Ocular Lesions.*—McLeod [188] describes some of the less common findings in the eyes in congenital syphilis. Lesions of the fundus may be divided into four main types:

*Type I.* The so-called "salt and pepper" fundus with yellowish, or grayish red dots interspersed among a multitude of granular brown to black pigment dots. In the more severe forms the spots are larger and tend to invade the macular region; the nerve may be atrophic and vision impaired.

*Type II.* Larger and more irregular pigment masses occur, located mostly at the periphery, between which similar "bleached" areas appear. The nerve may be atrophic. Sidler-Huguenin has noted this type after the subsidence of interstitial keratitis.

*Type III.* Disseminated chorioretinitis. The lesions are round or oval and appear as an atrophic patch surrounded by a ring of pigment. The macula may be involved.

*Type IV.* Similar to retinitis pigmentosa and at times difficult to differentiate. The visual symptoms are identical. This type seems now to be rare.

It is obvious that all these changes are dependent upon the migration of pigment consequent to inflammatory processes and as a natural result of the repair of localized lesions or in response to stimulation of the pigment cells as a part of the general defense mechanism of the body.

Anderson and Wilson [189] report the results of treatment with induced fever in 22 patients with interstitial keratitis. Seven had received previous chemotherapy, 6 of whom had shown no improvement after two to five months of treatment, and 3 of whom had lesions develop in the other eye during treatment. The seventh had had several relapses during a four year period of therapy. In 13 patients the keratitis was acute and untreated. Of these, 3 were given fever by injecting vaccine intravenously, and 10 were treated with malaria. Two of the 3 patients treated with vaccine and all of the 10 treated with malaria showed a satisfactory immediate response. There were two relapses, one six and one ten weeks after the induction of malaria. Both responded to a few injections of vaccine. Nine patients with chronic interstitial kera-

187. Wile, U. J., and Welton, D. G.: Prenatal Syphilis in One of Twins, Am. J. Syph., Gonor. & Ven. Dis. **22**:544 (Sept.) 1938.

188. McLeod, J.: The Eye in Congenital Syphilis, J. Missouri M. A. **36**:49 (Feb.) 1939.

189. Anderson, C. R., and Wilson, W. A.: Active Interstitial Keratitis of Late Prenatal Syphilis: Its Treatment, California & West. Med. **50**:196 (March) 1939.

titis were treated with fever. A satisfactory result was obtained in 3 with vaccine alone. Of the 6 remaining, 4 responded satisfactorily to malaria. The authors believe that their own results and those of other workers show that malaria is a valuable form of therapy in interstitial keratitis, particularly if followed by two years of chemotherapy.

*Treatment.*—Howard [190] shows that, unless neurosyphilis is present, the long term outcome of treatment in congenital syphilis is extremely satisfactory. Forty-five children were followed for two to ten years (average five to six years) after the completion of treatment. A satisfactory result was obtained for 85 per cent of the entire group, the result being better in those treated during the first year of life. Twenty children (45 per cent) were "cured." Eighteen children (40 per cent) had at the end of the ten year period a positive Wassermann reaction of the blood as the only sign of syphilis. The poor clinical outcome in the remaining 7 children was explained by the presence of neurosyphilis in 6.

*Epilepsy.*—Babonneix [191] investigated the association of epilepsy with congenital syphilis. Of 246 patients with congenital syphilis, 22 per cent had epileptic attacks. Among 323 persons with epilepsy selected at random and not previously known to have syphilis, 17 per cent were found to have congenital syphilis.

*Epiphysial Changes.*—Park and Jackson [192] present a correlation of roentgenologic and necropsy observations in congenital syphilis. In some infants the cartilage is most affected; in others, the osteoblasts. In some, destructive processes are predominant; in others, new bone formation in the periosteum. These irregular projections are not always present in children with congenital syphilis.

Necropsy studies show that the roentgenologically visible projections into the cartilage at the ends of the long bones are around the nutrient vessels of the cartilage, the cartilage canals. In many cases the proliferated cartilage shows extreme degenerative changes. The fundamental anatomic lesions may lie either in the cartilage canals or in the cartilage itself. The cartilage in close proximity to the cartilage canals is more normal than that lying at a distance, matures more quickly, becomes calcified earlier and so produces the irregular spike formation.

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190. Howard, P. J.: Congenital Syphilis: A Ten Year Study of Forty-Five Children, J. Pediat. **14**:220 (Feb.) 1939.

191. Babonneix, L.: Le rôle de la syphilis congénitale dans de déterminisme de l'épilepsie, Acta pædiat. **22**:47, 1938.

192. Park, E. A., and Jackson, D. A.: The Irregular Extensions of the End of the Shaft in the X-Ray Photograph in Congenital Syphilis, with Pertinent Observations, J. Pediat. **13**:748 (Nov.) 1938.

*Serologic Changes.*—Davies [193] carries further the work of Faber and Black [194] and of Christie [195] on a quantitative technic for testing the blood of infants of syphilitic mothers as an aid in differentiating syphilitic from normal children. Christie followed a group of newborn infants for four months and observed that infants whose blood tests, positive at birth, became negative and remained so presented subsequently no signs of syphilis but that infants whose tests showed an initial drop in titer and then a sudden rise showed later other signs of syphilis. Davies followed 56 infants for longer periods of time, 20 of them for one year. Of the 56 infants, 25 had positive neonatal blood tests; only 2 of these later showed congenital syphilis. Nineteen infants whose neonatal blood tests were negative were followed for six months, and 12 of the 19 were followed for one year; congenital syphilis developed in none.

In most instances the neonatal positive blood reactions (representing, of course, transfer of reagin from mother to fetus) diminished or disappeared within two weeks, but in 1 case the positive reaction remained for forty days and in another for three months. Davies suggests that inasmuch as congenital syphilis is more likely to develop in infants who have positive neonatal tests than in those whose tests are negative, infants with positive tests should be followed more closely and for a longer period of time.

*Oral Treatment with Acetarsone.*—One of the best of recent papers on the administration of acetarsone by mouth in the treatment of congenital syphilis is that of Pillsbury and Perlman.[196] Since 1931 these authors have treated 196 patients with this drug, for 187 of whom the diagnosis of syphilis seems certain. This group of 187 patients has been followed for periods varying from two months to six and a half years, and the observations form the basis of the present report. Of this number, 145 have been followed for more than one year, 116 for more than two years and 87 for more than three years since the institution of treatment. In 87 patients in this series syphilis was not diagnosed in the dispensary at the examination on admission and was

193. Davies, J. A. V.: The Evaluation of Serologic Tests for Congenital Syphilis, with Special Reference to the Neonatal Period, J. Pediat. **13**:341 (Sept.) 1938.

194. Faber, H. K., and Black, W. C.: Quantitative Wassermann Tests in the Diagnosis of Congenital Syphilis: Clinical Importance of Fildes' Law, Am. J. Dis. Child. **51**:1257 (June) 1936.

195. Christie, A. U.: Diagnosis of Syphilis in Newborn Infants: Use of Quantitative Wassermann Tests, Am. J. Dis. Child. **55**:979 (May) 1938.

196. Pillsbury, D. M., and Perlman, H. H.: Acetarsone Therapy in One Hundred and Eighty-Seven Cases of Congenital Syphilis, with Observations on a Group of Eighty-Seven Patients Receiving No Treatment, Arch. Dermat. & Syph. **39**:969 (June) 1939.

not discovered in subsequent examinations until, on an average, three years after admission. This group of patients, therefore, was one in which the course of the untreated disease could be observed, and the delay in the recognition of the disease explains why, although the average period of observation of the group of patients was four and four-tenths years, the average period of observation after treatment was begun was only two and eight-tenths years.

The authors are impressed with the clinical effects of treatment with acetarsone. In the 3 patients who were so studied the spirochetes disappeared from surface lesions in seventy-two, ninety-six and one hundred and twenty hours, respectively. In general, cutaneous lesions healed within three or four weeks; osseous lesions responded satisfactorily, and in 2 patients with Clutton's joints involution occurred. They observed no instance of late clinical relapse after treatment with acetarsone, and clinical progression in spite of treatment occurred in only 8 cases. The effect of the drug on interstitial keratitis was, however, disappointing.

A very satisfactory incidence of serologic reversals was obtained, i. e., 70 per cent reversals in children whose treatment was instituted before they were 6 months of age, and 36 per cent reversals in children who were more than 6 months of age when treatment was begun. The authors point out, however, that this is less frequent serologic reversal than that reported by Smith for children treated with alternating courses of a bismuth preparation and an arsphenamine. They do not, however, consider the possible effects of differences in the serologic laboratories and in the sensitivity of the serologic tests employed.

Their experience with the incidence of reaction emphasizes one of the aspects of any method of oral treatment for syphilis which is extremely distressing; i. e.: Can the parents or guardians be depended on to administer the drug with the regularity which is so necessary? With the therapeutic system which they were using, Pillsbury and Perlman found that some type of reaction developed in 32 per cent of children being treated with acetarsone in the hospital wards whereas only 8 per cent of those whose treatment was being prescribed in the outpatient department, to be carried on at home, suffered the same fate. Since they could find no other factor to explain so wide a difference in the incidence of reactions, they were forced to conclude that the basic dose which they employed was perhaps too high and that the children being treated in the hospital were receiving it as prescribed while those being treated in the outpatient department were not. Concerning this they say:

> . . . We cannot but feel, however, that a specter is always present—that the entrusting of treatment to a prescription blank may shift the responsibility for treatment of an entirely helpless and dependent child to the hands of an irrespon-

sible parent or guardian. It is true that one can sense the irresponsible parent quickly, and we believe that he is an absolute contraindication to further acetarsone therapy. The child with congenital syphilis has already paid too great a price for the irresponsibility of one of his parents; no more should be expected of him.

The cerebrospinal fluid was examined in 102 cases, with positive results in only 2; in 2 others, however, there were clinical signs of neurosyphilis. In 1 of these there was said to have been an abnormal reaction of the cerebrospinal fluid previously.

In the discussion the authors point out that there is no adequate experimental background for the determination of the toxicity and spirocheticidal effect of individual lots of acetarsone. This is due, in part at least, to differences in the factors which influence absorption from the gastrointestinal tract of man and of experimental animals; but other reasons are probably also involved. They feel that acetarsone by mouth is an active antisyphilitic agent, which is, however, less rapid in its action than arsphenamine. In clinical use they feel that a dosage based on weight is essential, but even with such a dosage reactions are not entirely prevented. Nephritic reactions occurring insidiously and suddenly are the greatest single drawback to treatment with acetarsone, and it is strongly believed that administration of the drug should not be resumed after such a reaction.

The authors summarize the objections to this method of treatment as follows:

> The effect of acetarsone in arresting congenital syphilis is inferior to that of arsphenamine and bismuth preparations. The incidence of reactions is high; acetarsone cannot be controlled by experimental studies of spirocheticidal action and toxicity in animals, and administration to outpatients is not assured.

### ACQUIRED SYPHILIS IN CHILDREN

From several large eastern clinics Smith[197] has collected 125 cases of acquired syphilis in children, 10 years of age or younger, and has analyzed them from the standpoint of mode of infection. This was attempted sexual intercourse in 43, kissing in 15, household contact in 14, transfusion in 9 and unknown (no data) in 44. Forty-five of the 125 children were admitted, from 1920 to 1937, to the pediatric clinic of the Johns Hopkins Hospital. Comparing this number with the 1,025 admitted for congenital syphilis over the same period, he finds the ratio of acquired to congenital syphilis in children under 10 years of age to be 1:23. Again comparing this group with the 4,487 patients with early syphilis admitted to the clinic for adults he finds that the ratio of acquired syphilis in children to that in adults is 1:100. Acquired

197. Smith, F. R., Jr.: Acquired Syphilis in Children: An Epidemiologic and Clinical Study, Am. J. Syph., Gonor. & Ven. Dis. **23**:165 (March) 1939.

syphilis is probably more common in children than is suspected. Waugh [198] also reviews the literature on acquired syphilis in children and analyzes the data on 35 children seen from 1931 to 1936 in the venereal disease clinic of the United States Public Health Service at Hot Springs, Ark. Twenty-two children were between 5 months and 10 years of age, 2 were 11 years old, and 11 were 12 to 14 years of age. Only 2 of the group between 5 months and 11 years of age acquired syphilis through sexual intercourse, but all of the age group from 12 to 14 years of age acquired the disease through sexual exposure. Schoch and Long [199] report the observation of acquired syphilis in 4 sisters 6, 8, 9 and 11 years of age. All acquired syphilis from sexual exposure to the same 17 year old boy.

### SYMPOSIUM ON SYPHILIS

At the 1938 meeting of the American Association for the Advancement of Science in Indianapolis, there was presented a symposium on syphilis consisting of thirty papers which have subsequently been published in monograph form.[200] Since the essayists in this symposium addressed themselves to reviews of assigned topics, there is comparatively little emphasis on the presentation of original investigation. A bibliography of each paper presented is therefore not supplied, though the symposium, both because of its distinguished contributors and because of the nature of their contributions, is in itself a valuable review of the literature of syphilis.

A general introduction to the symposium and some consideration of the biology of syphilitic infection were provided by Chesney. Holcomb presented the evidence against the American origin of syphilis, and Pusey defended the opposite point of view. The perennial debate as to the identity of syphilis and yaws was continued, with Butler upholding the affirmative and Fox the negative. Hudson discussed the significance of bejel. Ingraham's paper was concerned with S. pallida and the etiology of syphilis, while Olsen discussed the life cycle of S. pallida. Turner presented a description of the interrelationship between S. pallida, Spirochaeta pertenuis and Spirochaeta cunniculi.

A description of experimental syphilis and of the transmission of the disease to animals and their clinical reaction to it was in the capable hands of Pearce, while Beerman discussed the problem of treatment-resistant strains of S. pallida.

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198. Waugh, J. R.: Acquired Syphilis of Infancy and Childhood: Report of Thirty-Five Cases, Am. J. Syph., Gonor. & Ven. Dis. **22**:607 (Sept.) 1938.

199. Schoch, A. G., and Long, W. E.: Acquired Syphilis in Children: Case Reports on Four Sisters, Am. J. Syph., Gonor. & Ven. Dis. **23**:186 (March) 1939.

200. Moulton, F. R.: Syphilis, Occasional Publications of the American Association for the Advancement of Science, no. 6, Lancaster, Pa., The Science Press, 1938.

Eagle and Mendelsohn presented a summary of Eagle's work on the spirocheticidal action of the arsphenamines on S. pallida in vitro. The immunity acquired in patients and the resistance acquired in the rabbit were the subject allotted to Kemp, while Michelson presented the newer conceptions concerning the pathologic aspects of syphilis.

From the clinical standpoint there were discussions of (1) methods for estimating the outcome of neurosyphilis (by O'Leary), (2) syphilis in pregnancy (by Beckh and Daily), (3) congenital neurosyphilis (by Dennie), (4) cardiovascular syphilis (by Scott) and (5) the clinical aspects of syphilis in diagnosis (by Senear).

The serologic aspects of the disease were not slighted, and the present status of serologic tests for syphilis was described by Hartman and Yagle, while the inseparable serologic twins, Kahn and Kline, discussed, respectively, outstanding features of the Kahn antigen, and the Kline antigen for the microscopic slide precipitation tests for syphilis. Kolmer's paper, however, was devoted not to a consideration of his own test but to serologic reactions in general and immunity in relation to cussed, respectively, outstanding features of the Kahn antigen, and the

From the therapeutic standpoint, Solomon discussed problems in specific and nonspecific treatment of neurosyphilis, Tatum devoted himself to some of the aspects of the chemotherapy of syphilis, and Wieder described the clinical status of the antisyphilitic drugs.

Untoward reactions to treatment were discussed by Kampmeier, and D. C. Smith attempted to evaluate the role of intercurrent infections in untoward cutaneous reactions following the administration of arsphenamine.

The papers on the public health aspects of syphilis control were contributed by Wile and Parran.

The volume in which this symposium is published is a valuable addition to the library of any physician particularly interested in the field of syphilis.

# News and Comment

## GENERAL

**Directory of Medical Specialists.**—The first edition of the *Directory of Medical Specialists,* listing approximately 14,000 specialists certified by the twelve American boards and the two affiliate boards in the specialties, will be issued by the Advisory Board for Medical Specialties in December. It will be the official publication of the American Board for Medical Specialties and will contain, without expense to them, only the names of those specialists who have been certified by the American boards. It is expected that the directory will be issued every two years.

The directory will contain three sections: (1) a brief description of the Advisory Board for Medical Specialties, its organization and its objectives; (2) a description of the individual boards, with a geographic and a detailed biographic listing of their diplomates, the requirements for admission to their examinations for certification, the details of their organization and other general information, and (3) a complete alphabetic list of all 14,000 diplomates, with their addresses and indications of certification in their specialties.

The editorial board consists of the secretaries of the fourteen American boards. Dr. Paul Titus, 1015 Highland Building, Pittsburgh, secretary of the Advisory Board for Medical Specialists, is the directing editor.

The project is not designed to be profit making; hence the subscription price has been set at $3.50 a copy, which is computed to cover only publication expenses. Subscriptions may be sent to the publication office, Columbia University Press, 2960 Broadway, New York, or to the office of the directing editor.

# Notices

## CUMULATED INDEX OF THE ARCHIVES OF INTERNAL MEDICINE

Requests have been received for a twenty year index of the ARCHIVES OF INTERNAL MEDICINE. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $5 a copy. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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# Book Reviews

**Fundamentals of Internal Medicine.** By Wallace Mason Yater, A.B., M.D., M.S. (in Medicine), Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine; Physician in Chief, Georgetown University Hospital; Physician in Chief, Gallinger Municipal Hospital, Washington, D. C., and Former Fellow in Medicine, the Mayo Foundation, Rochester, Minn., and collaborators. Cloth. Price, $9. Pp. 1021, with 255 illustrations and charts. New York: D. Appleton-Century Company, Inc., 1938.

During the past few years a number of textbooks of internal medicine have been presented to the medical profession. All of them represent a great deal of painstaking work and meticulous attention to detail on the part of the authors. Many of them have been good—most of them acceptable—but is this effort worth the result that is attained? Is there need for this multiplicity of textbooks of internal medicine? By what criteria shall we rank one above the other?

Dr. Yater states that this book is "designed primarily for the introduction of students to the subject of internal medicine." This, of course, must be the function of all such textbooks, and it is the necessity for brevity that makes the selection of material so important. If this necessity is kept in mind, Dr. Yater has compiled a good book.

It is written in semioutline form, and the important data are set in heavy black type. Each section of the book is preceded by an outline of the material contained therein and is followed by a list of recommended texts for additional reading. It is this extreme condensation of material that constitutes the greatest objection to the work. Most of the important points dealing with any disease are mentioned, but they are not and cannot be adequately discussed. Syphilitic heart disease is covered in three pages. Pulmonary tuberculosis receives twenty pages—a generous allowance. Diabetes mellitus is discussed in five pages.

By way of contrast, almost one quarter of the book is devoted to a consideration of nervous and mental diseases and diseases of the eye and ear. In view of their adequate treatment elsewhere, one wonders if these subjects should be granted a place in a textbook of internal medicine.

It is, perhaps, unfair to direct all this criticism at Dr. Yater's book when it is equally applicable to similar books. As an outline of internal medicine the work is excellent. An adequate discussion of disease will not be found here. One cannot help but feel that Dr. Yater's unusual ability should have been employed to better advantage than in the production of just another textbook of internal medicine.

**Insulin: Its Chemistry and Physiology.** By Hans F. Jensen, Ph.D. Price, $2. Pp. 252. New York: Commonwealth Fund, 1938.

This monograph is a timely and important addition to the literature on insulin and carbohydrate metabolism. The purpose of the author, as stated in the preface, was "to give a comprehensive review of the latest developments in the chemical and physiological investigations of insulin." This purpose has been admirably achieved.

In the first chapter the history of the investigations which culminated in the recognition of the relation between the islands of Langerhans and human and experimental diabetes is surveyed, along with mention of some of the early attempts to prepare active extracts of the pancreas (some of these extracts undoubtedly contained insulin), which were made prior to the successful solution of this problem by Banting and Best in 1921. After this are chapters on the preparation and purification of insulin, the chemistry of insulin as elucidated by the study of crystal-

line insulin, the standardization of insulin, modes of administration and prolongation of the action of insulin by such means as admixture with protamines, the use of insulin substitutes, duodenal extracts and guanidine derivatives and the physiologic action of insulin.

The investigation of crystalline insulin, much of which has been done by Dr. Jensen himself, indicates that it must be regarded as a typical protein, the composition of which does not differ markedly from that of any other protein. It represents "the first instance in which a protein possessing a specific physiological action has been obtained in crystalline form" and as such has become probably the most thoroughly investigated of all the proteins. The results of these researches indubitably connect the physiologic action of insulin with certain chemical groups in the molecule, but attempts to associate physiologic activity with a special prosthetic group, like that in hemoglobin, have failed. Several peptids containing some of the groups have been synthesized, but none of the synthetic compounds has possessed hypoglycemic activity.

To many the chapter on the physiologic action of insulin will be of most interest and importance. Here fifty-four pages of text summarize the work reported in 624 papers, which are listed in forty-five pages of bibliography. After consideration of this vast amount of material, the author takes the position that "neither the nonutilization nor the overproduction theory can completely explain the symptoms of diabetes" and that "carbohydrate metabolism is controlled by the physiological coordination of various active agents in the body . . ." In regard to the action of insulin he says: "The precise mechanism of the physiological action of insulin has yet to be fully explained."

The bibliography is well selected, and there are, in addition, both author and subject indexes.

**Parasitology, with Special Reference to Man and Domestic Animals.** By Robert Hegner, Francis M. Root, Donald L. Augustine and Clay G. Huff. Price, $7. Pp. 812. New York: D. Appleton-Century Company, Inc., 1938.

This text is a revised edition of "Animal Parasitology" (1929) written by Hegner, Root and Augustine. The text, over 700 pages, consists of an introductory chapter on parasitism, a section of fifteen chapters on protozoology by Robert Hegner, a section of sixteen chapters on helminthology by Donald Augustine and a section of twenty-two chapters on the arthropods of parasitologic importance by the late Francis Root, revised by Clay Huff. The text has been revised for the use of students in colleges, universities, medical schools and schools of hygiene, public health and tropical medicine.

In most instances the material contained in this treatise is accurate. In an attempt to include information with regard to the less important parasites the authors have neglected the more important phases of parasitology. This is especially noticeable in the chapter on amebas. Seven pages have been devoted to the amebas of lower animals and seven pages to the methods of obtaining and preparing the parasites for study. Of the latter, six pages are devoted to the iron-hematoxylin method of staining and to the culture of amebas. Both of these procedures are too technical for the audience for whom this book is intended. The procedures for diagnosis and treatment are in instances too abstract.

Because of the broad scope of this text, with special reference to lower animals, it will probably not be used as a study guide for medical students. However, because of its voluminous bibliography and comprehensive treatment of the subject matter it is recommended as a reference for that group.

**What a University President Has Learned.** By A. Lawrence Lowell, President Emeritus of Harvard University. Price $1.75. Pp. vi + 150. New York: The Macmillan Company, 1938.

This book contains eight short essays which should be read by any one interested in education. Mr. Lowell's way of saying things is clearcut and positive, and what he has learned as a university president is worth reading.

Although none of Mr. Lowell's discussions deal primarily with the problems of medical education, he has many wise and witty remarks about education in general that are applicable to medicine. To readers who enjoy a pungent, almost epigrammatic style the book will be a constant delight. Sentences like these are typical. "In mental as in physical instruction the question is largely one of appetite and of how this can be whetted." "Examinations like most human things are imperfect and their results are only approximate." "The choice of a career is less important than is commonly supposed. Much the same qualities are required in all professions and in all kinds of business—intelligence, good judgment, fair dealing and above all diligence with a determination to make good by work well done. Without these a man rarely succeeds in any career; with them there are an abundance of niches in almost every serious occupation."

All medical students and their teachers will find these essays stimulating.

**Iodine Metabolism and Thyroid Function.** By A. W. Elmer, M.D. Price $10. Pp. 605, with 23 figures and 86 tables. London: Oxford University Press, 1938.

This book is an excellent review of the subject of iodine metabolism and includes a lengthy and comprehensive bibliography in which references as recent as 1938 may be found.

After a brief historical introduction the various methods of iodine determination are presented. The remainder of the book is divided into two sections, in which are discussed the physiology and the pathology of iodine metabolism. The author not only is thoroughly conversant with the experimental and clinical research in this field but has made a number of noteworthy contributions as a result of his own investigations. He describes in detail and evaluates the experimental work dealing with the various aspects of iodine metabolism, especially as related to the thyroid gland. Disputed questions are presented impartially, and the opportunities for further investigation are indicated.

The book represents a vast amount of careful study and should be extremely valuable as a summary and reference to the biochemist and the physiologist, as well as to the clinician who is interested in fundamental problems related to the thyroid gland.

**Scarlet Fever.** By George F. Dick, M.D., Professor of Medicine, University of Chicago, and Gladys U. Dick, M.D. Price, $2. Pp. 149, with 8 colored plates and 4 charts. Chicago: The Year Book Publishers, Inc., 1938.

This small monograph is well done. It tells the story of scarlet fever clearly and in a readable fashion. The book starts with a history of scarlet fever; chapters follow dealing with the etiology of the disease, its pathology, its clinical manifestations and its diagnosis, prognosis and treatment.

Naturally the authors have a good deal to say about cutaneous testing, susceptibility to scarlet fever, immunization against the disease and antitoxin treatment for it. The volume ends with an excellent list of references to current literature. Finally, there is a good index.

All medical students will like the book, and general practitioners, too, will find it readable if they wish to brush up on what is known of scarlet fever. The eight colored plates are good. If one were critical one might object to the two depicting the "strawberry" and the "raspberry" tongue, but, on the whole, every one realizes that the authors know scarlet fever as well as the disease can be known. It is a pleasure to have their views so clearly and simply presented.

**Kaffee und Kaffein.** By O. Eichler, M.D. Price, 8.70 marks. Pp. 160. Berlin: Julius Springer, 1938.

This book contains the material presented in the symposium on coffee and caffein at the meeting of the German Pharmacologic Society in Berlin in 1938

The original papers by W. Straub, O. Eichler and W. Stepp appeared in *Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie* (**190**: 118-170 [Sept.] 1938). Aside from the exhaustive way in which the literature in the field is presented (484 references), the chief value of the book lies in the highly critical way in which the author attempts to evaluate published and often accepted "facts" and in his presentation of unsolved problems.

The book has chapters on the history and preparation of coffee as a beverage, on the actions of coffee and caffein on the central nervous system, circulation, kidneys, metabolism and organs of reproduction and on caffeinism and tolerance. There is an interesting discussion of the action of caffein during muscular exercise.

This publication is timely, since the subject has—to the knowledge of the reviewer—not been presented in comprehensive form since J. Bock's article in Arthur Heffter's "Handbuch der experimentellen Pharmakologie" (Berlin: Julius Springer, 1920).

**Physikalische Therapie.** By H. Lampert. Price, 15 marks. Pp. 250. Dresden: Theodor Steinkopff, 1938.

This is the twenty-fifth volume of a series of monographs on various subjects for the "practicing physician." The subject of this volume is physical therapy.

The author has covered the entire field of physical treatment, which has now attained extensive proportions. Accordingly, in a 250 page monograph it is possible to include all the developments in this type of therapy in compendious form only. Whereas such a condensation obviously results in loss of certain details, nevertheless the book is of value to the general practitioner as a reference and as a means of rapidly obtaining general information concerning this type of therapy.

The rationale of the various forms of physical therapy, such as hydrotherapy, massage, exercise, application of light and of radium and electrotherapy, is discussed briefly. Their indications and technics are described. The book is profusely illustrated with charts, diagrams and photographs. A complete index, in which the prominent subjects are printed in bold type, is helpful. A more complete bibliography would increase the value of the book as a reference.

**Le duodenum, atlas de radiologie clinique.** By P. Cottenot, Max Lévy and E. Chérigié. Price, 285 francs. Paris, France: Gaston Doin & Cie, 1938.

This study of the duodenum, presented in atlas form, includes all of the diagnostic problems, frequent and rare, which the clinical roentgenologist may encounter in his daily practice. The roentgenograms shown are supplemented by self-explanatory diagrams, ample text and, in some instances, case histories. Adequate attention is given variations of the normal duodenal picture, anomalies, changes engendered by extraduodenal pathologic conditions, changes resulting from pressure of neighboring structures, diverticula, stenosis, duodenitis, tumor, ulcer and postoperative conditions of the duodenum.

The occurrence of definite clinical manifestations attributable to diverticula is contrary to general experience. Functional conditions, although they are discussed in relation to other topics, are not given a separate chapter, which their importance, in my opinion, justifies.

This work should be of definite practical value to roentgenologists.